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SYNTHETIC STUDIES ON TANDEM NAZAROV/5-*EXO* RADICAL CYCLIZATION AND ON POLYHYDROXY AMPHOTERICIN B MIMICS DERIVED FROM CARBOHYDRATES

by

CRAIG JAMES RAILTON, Jr

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING 1995

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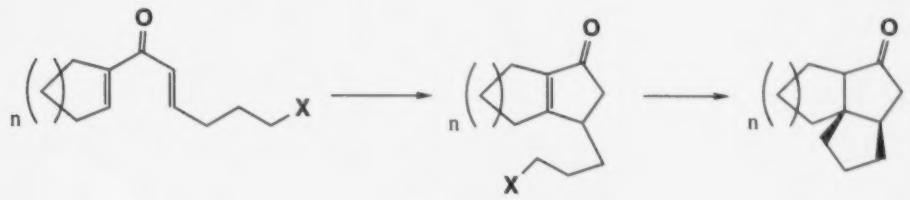
To my Family

ABSTRACT

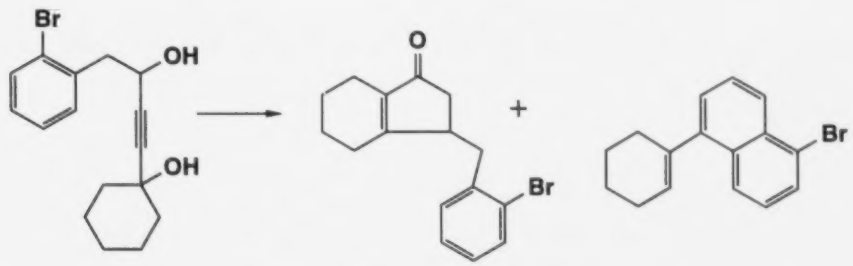
Studies towards (a) the development of a general method for tandem Nazarov/5-*exo* radical cyclization and (b) towards the preparation of polyhydroxy Amphotericin B mimics are described in this thesis.

The planned reaction sequence for tandem Nazarov/5-exo radical cyclization is illustrated in Scheme 1.



Scheme 1

It was found that the phenylseleno functional group interferes with the Nazarov cyclization; although, suitable substrates for the reaction sequence could be made from acetylenic diols as shown in Scheme 2. However, this type of

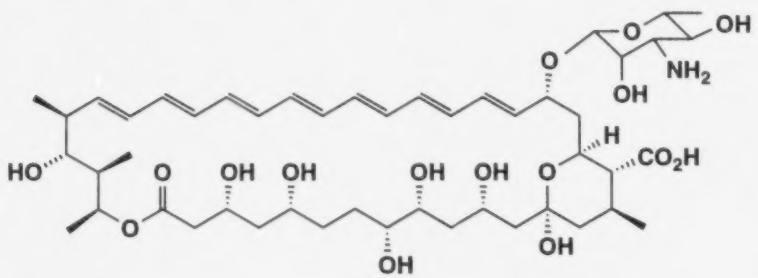


44 45 47

Scheme 2

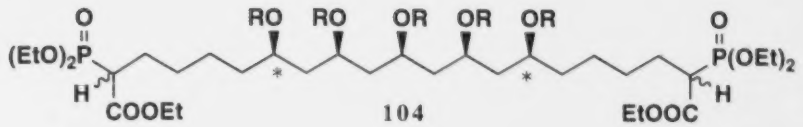
substrate (**44**) leads also, in the Nazarov reaction, to a side product of structure **47**. In addition to the use of acetylenic diols, reaction sequences based on Friedel-Crafts acylation, Shapiro reaction, Horner-Emmons reaction, and ketene thioacetals were examined.

Studies toward the synthesis of mimics of Amphotericin B (**60**), were also carried out. The types of mimic to be

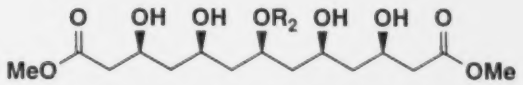


60

prepared would retain the macrocyclic ring, the elongated shape, the system of conjugated double bonds, and a hydrophilic polyhydroxy chain. Both 1,3-polyhydroxy chains and 1,2-polyhydroxy chains derived from carbohydrates were prepared. Two 1,3-polyhydroxy precursors, compounds **104** and **113** of similar structure (as shown below) were made, using methods based on literature procedures.



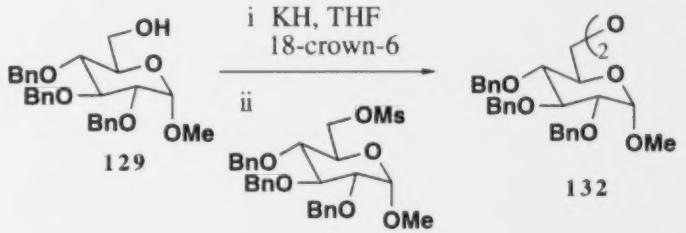
104



R = TBDMS
R_2 = TIPS

113

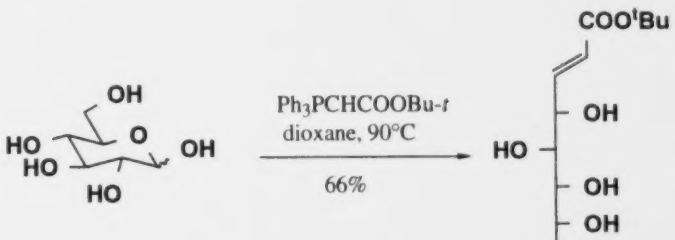
A procedure was developed to allow the coupling of carbohydrates at the C-6 position via an ether linkage to give 6',6-anhydrodisaccharides, such as **132** (Scheme 3).



129 131 132

Scheme 3

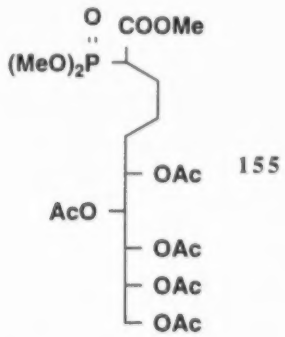
A chain extension procedure for unprotected carbohydrates was also developed; an example is summarized in



152

Scheme 4

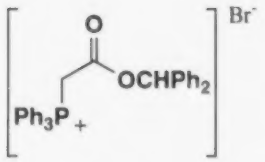
Scheme 4. The chain extension was used to demonstrate how Barton decarboxylation and subsequent radical Michael addition could be used to afford the phosphonate **155**, shown below.



155

Compound **155** is related to key intermediates required for double Wadsworth-Horner-Emmons reactions that could be used to prepare the macrocyclic mimics mentioned above.

The new method for preparation of higher order monosaccharides, based on Wadsworth-Horner-Emmons chain extension to give α,β-unsaturated esters (Scheme 4), was extended to six different sugars. A second reagent, compound **170** (Scheme 5), was designed and used on three different sugars to allow deprotection of the carboxylic acid and removal of the olefin in one step by hydrogenation. The utility of the new method was demonstrated by preparation of lactone **174** (Scheme 5), thereby completing a formal synthesis of KDO (**175**).



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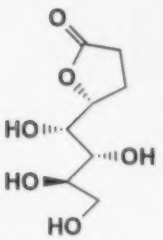

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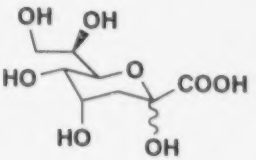

KDO, 175

Scheme 5

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Part I

I. Tandem Nazarov/5-*exo*-Radical Closure

Introduction

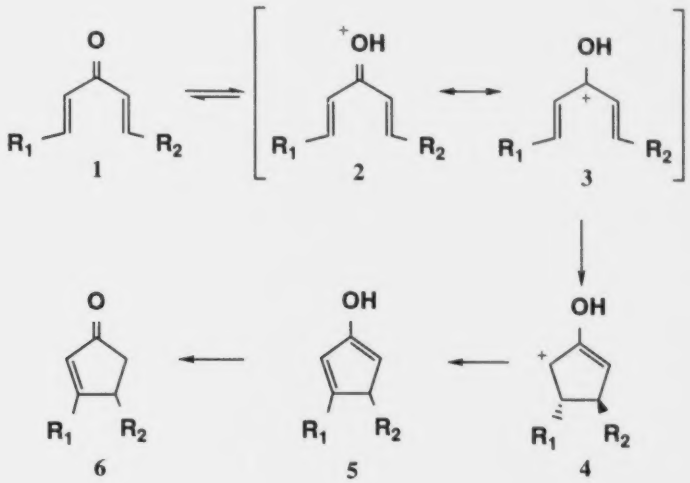
I.1. General Introduction.

There has been an ongoing program in our laboratory to combine, in a tandem fashion, 5-*exo* radical cyclization with other well-established reactions that generate olefins. Several reactions have been successfully coupled with 5-*exo* radical cyclization, and these include the Diels-Alder reaction,[1,2] the Claisen rearrangement,[3] and the Pauson-Khand reaction.[4] The tandem coupling of two reactions is a useful process because it allows rapid construction of complex systems. We wished to investigate the possibility of including the Nazarov reaction in this group of tandem processes, so that the product of a Nazarov cyclization would be correctly constituted for direct radical closure.

I.2 Nazarov Reaction.

Rearrangement of allyl-vinyl and divinyl ketones to cyclopentenones was first reported by Nazarov and co-workers in a series of papers.[5,6,7] The mechanism of the Nazarov reaction was demonstrated by Shoppee and co-workers.[8] to involve an intramolecular electrocyclization In Scheme 6, the protonated divinyl ketone **2** is a resonance form of hydroxypentadienyl cation **3**, which is a 4π electron system.

The cation undergoes thermal conrotatory ring closure (disrotatory photochemically) to afford cyclopentene cation **4**. This then loses a proton to form dienol **5**, which tautomerizes to the final cyclopentenone **6**.

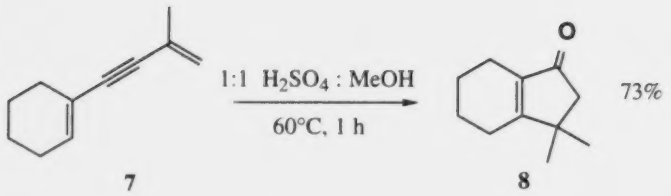


Scheme 6

There are two extensive reviews[9,10] on the Nazarov reaction, which give many examples of how it has been used and the types of substrates that are suitable. The following examples have been chosen from the literature to illustrate the wide variety of appropriate substrates.

I.2.a. Cyclopentenones from 1,5-Dien-3-ynes.

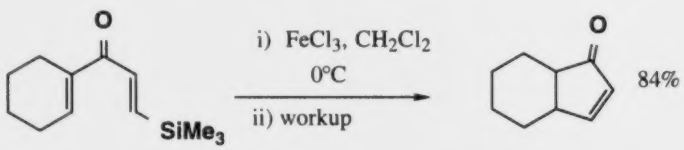
A good example (Scheme 7) of a 1,5-dien-3-yne that was used to prepare a cyclopentenone comes from the work of Nazarov and Kotlyarevskii.[11] Treatment of **7** with 1:1 H_2SO_4-MeOH at 60 °C, gave the fused cyclopentenone **8**.



Scheme 7

I.2.b. Cyclopentenones from Divinyl Ketones.

When divinyl ketones are treated with either Brönsted or Lewis acids, they undergo ring closure to the cyclopentenone system. Usually, the carbon-carbon double bond of the enone is located in the thermodynamically most stable position. However, Denmark and co-workers have developed a methodology which takes advantage of the ability of silicon to stabilize a β positive charge, and this effect can be used to give products with the carbon-carbon double bond in the thermodynamically less stable position,[12] as seen in Scheme 8.

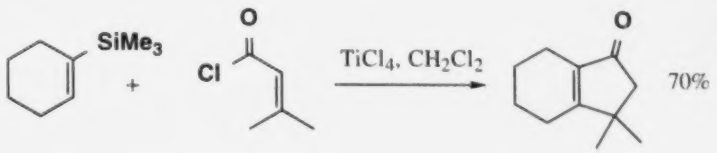


Scheme 8

I.2.c. Cyclopentenones by Friedel-Crafts Acylation.

Friedel-Crafts acylation has also been used to prepare cyclopentenones. An olefin or a trialkylstannyl- or trialkylsilyl-substituted olefin is treated with an α,β-unsaturated acylating agent in the presence of a Lewis acid.

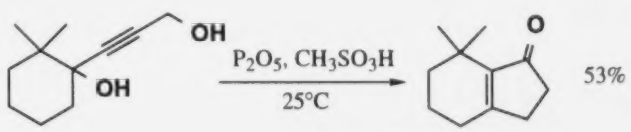
These reaction conditions afford a divinyl ketone which then cyclizes in the presence of the Lewis acid. An example of such a process is shown in Scheme 9.[13]



Scheme 9

I.2.d. Cyclopentenones from Acetylenic Diols.

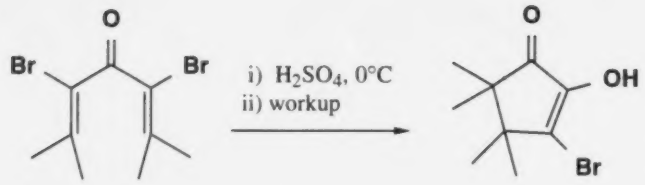
Acetylenic diols have been used in Nazarov cyclizations. The mechanistic pathway involves first a Rupe rearrangement,[14] then elimination of water, to give the dienone. A conrotatory electrocyclic ring closure of the dienone follows, to give the cyclopentenone (Scheme 10).[15]



Scheme 10

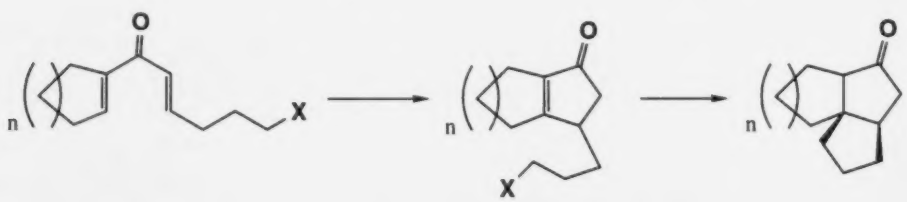
I.2.e. Nazarov Reaction with Substrates containing Heteroatoms.

There is one example (Scheme 11) in the literature of a Nazarov reaction in which a bromine is present in the substrate.[16]



Scheme 11

This example was encouraging because we wished to combine the Nazarov reaction with the well-known process of 5-*exo* radical cyclization and, to do this, it would be necessary for the substrate to carry a homolyzable group such as a halogen or a phenylseleno unit. The heteroatom would need to be located in a suitable position to allow cyclization onto the β carbon of the enone that is formed by Nazarov reaction, as shown in Scheme 12.



Scheme 12

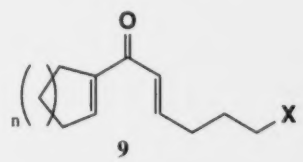
For this scheme we needed to find a heteroatom X as well as reaction conditions that would tolerate its presence during the Nazarov cyclization process.

Tandem Nazarov Cyclization/5-*Exo* Radical Closure

Results and Discussion

II.1. Introduction.

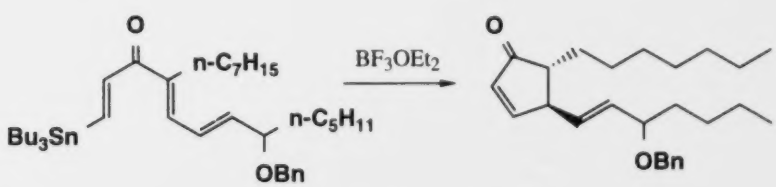
In order to carry out the desired process of tandem Nazarov cyclization/5-*exo* radical closure, a dienone of general structure **9**, or an equivalent substrate that would allow generation of **9** in situ, would be required, and we examined a number of processes that might lead to such compounds.



9

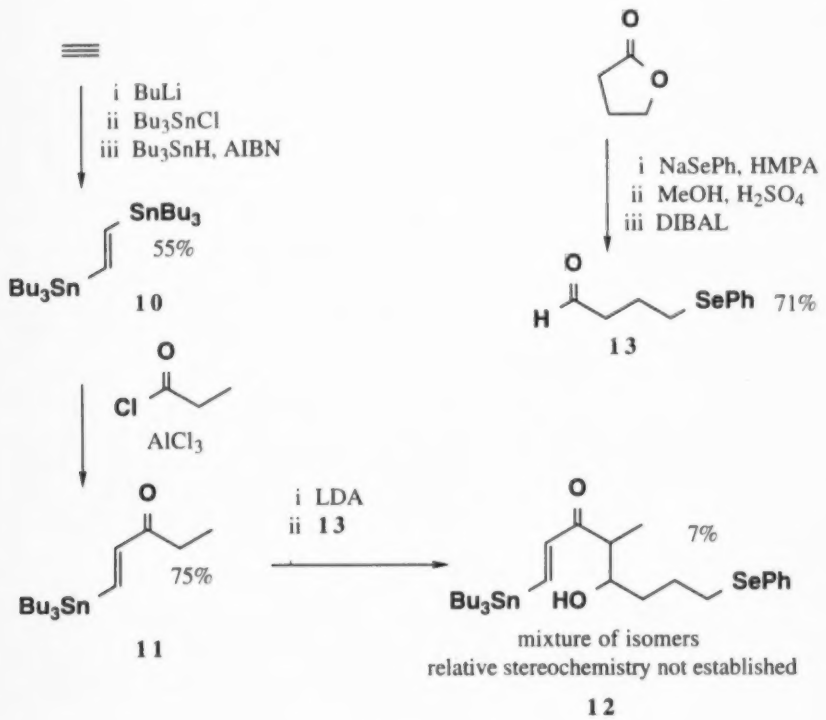
II.2. Use of Vinylstannanes

The first synthetic route tried was based on work by Johnson and Peel in which a prostaglandin derivative was prepared (Scheme 13).[17] They had incorporated a benzyloxy substituent at the same position that we wished to place the homolyzable group.



Scheme 13

It was decided to simplify the substrate by removal of the heptyl and pentyl side chains as well as the double bond closest to the benzyloxy group. The benzyloxy substituent was also replaced with a phenylseleno group which would act as the radical source. To this end, the following sequence of reactions was carried out (Scheme 14).



Scheme 14

Distannylethylene **10** was prepared by the method of Seitz and co-workers[18] and subsequent Friedel-Crafts acylation[13,19] gave compound **11**. However, compound **11** was unstable to chromatography and so we used unpurified material for the next step. To add the chain bearing a homolyzable

substituent, an aldol reaction was used. The required phenylseleno aldehyde **13** was prepared from γ-butyrolactone using the method of Dowd and Kennedy,[20] as modified by R. Bergstra of this laboratory.[21] The low yield in the aldol reaction is due to the fact that the compound decomposed to unidentifiable material during purification. The crude vinyl stannane **12** was contaminated with tin species which could be removed only by flash chromatography, using a solvent system containing triethylamine. The yield of **12** was only 7% and so this approach was not pursued.

II.3. Use of the Shapiro Reaction.

Paquette and co-workers[13] and Denmark and co-workers[22, 23] have both used carbanion chemistry to prepare dienols of general structure **14** (Scheme 15). Thus, compounds of type **14** were obtained by addition of a vinyl anion[13] or a vinyl Grignard reagent[22,23] to an α,β-unsaturated aldehyde.

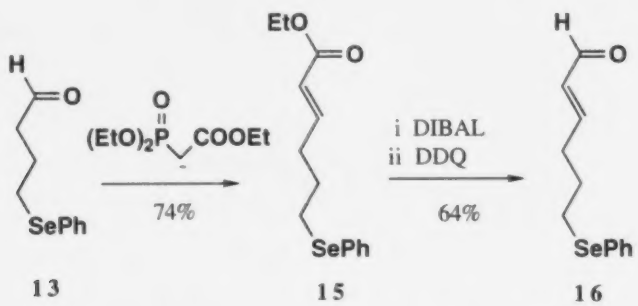
14

Scheme 15

We decided to try the Shapiro reaction to generate a vinyl anion, which would then be allowed to react with an α,β-unsaturated aldehyde bearing a phenylseleno group. Our decision to use the phenylseleno group as the radical

precursor restricts the number of oxidizing agents available to oxidize the dienol to the dienone.[24]

The required α,β-unsaturated aldehyde **16** was prepared from compound **13** by Horner-Emmons olefination (Scheme 16). Reduction of the resulting ester **15** to the alcohol was accomplished with DIBAL, and oxidation to aldehyde **16** was then done with DDQ.



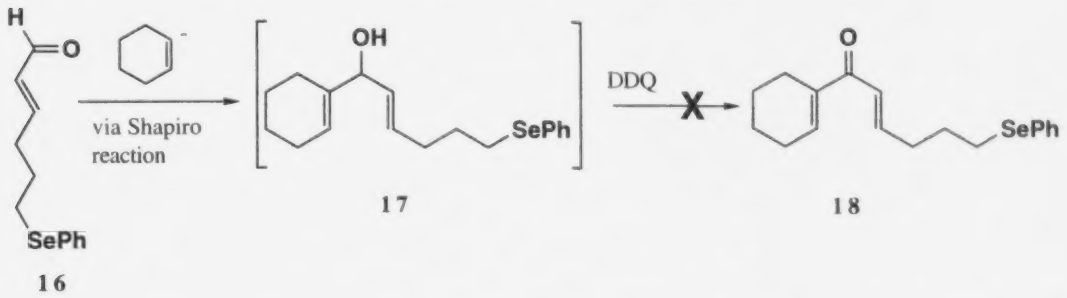
13 15 16

Scheme 16

It was later found that the two step reduction - oxidation sequence was unnecessary because, if great care was taken to keep the reaction temperature at -78 °C throughout the process, including workup, then ester **15** could be reduced directly to aldehyde **16** with DIBAL.

Alkylation was attempted using the cylcohexenyl anion, prepared from cyclohexanetosylhydrazone and *n*-BuLi.[25,26,27,28] The desired dienol **17** was formed, but not isolated, because it appeared to be unstable to chromatography (2D TLC). DDQ was used for the oxidation step instead of NiO_2 or $Ba(MnO_4)_2$, which had been used by Denmark[22] and others,[27] since we were

not sure that these reagents were compatible with the phenylseleno group in **17**. The oxidation did not afford the desired dienone **18** (Scheme 17).



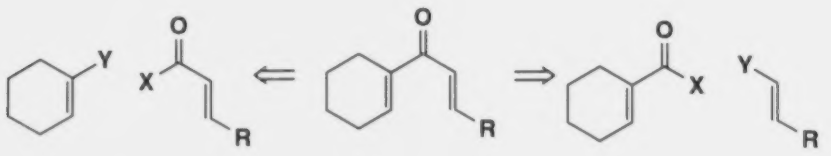
16 17 18

Scheme 17

We also thought of using a vinyl Grignard reagent as the source of the anion; however, attempts to prepare 1-bromocyclohexene on a large scale, using Caubere's method,[29,30] did not afford pure material (needed for the Grignard reaction) since the product was usually contaminated with about 30 mol % of 3-bromocyclohexene. When vinylmagnesium bromide was allowed to react with **16**, the required product was formed in low yield, and attempts to oxidize the dienol to the dienone were again unsuccessful. Because of the problems with the oxidation and the instability of the intermediate dienols, this approach was not taken further.

II.4. Use of the Friedel-Crafts Reaction.

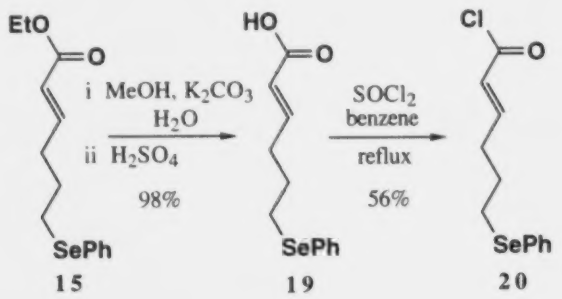
There are many examples of the use of the Friedel-Crafts acylation to prepare cyclopentenones. There are two possible disconnections for the type of system we needed (Scheme 18).



Scheme 18

In Scheme 18 the identity of **X** is usually a halogen and **Y** is usually a hydrogen, trialkylsilyl or trialkylstannyl unit. The choice of the stannyl and silyl groups usually allows milder conditions, especially lower temperatures, to be used.

The left hand disconnection was tried first because a good supply of ester **15** was available. The compound was transformed (Scheme 19) into the corresponding acid chloride



Scheme 19

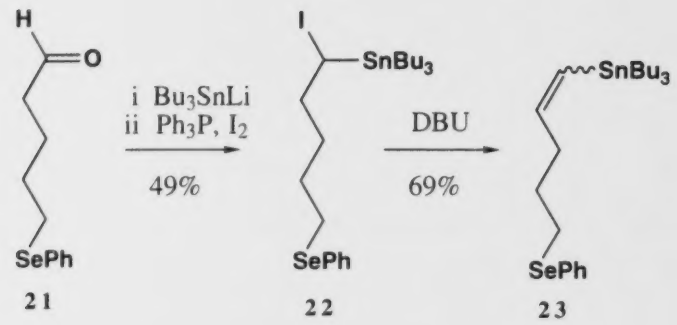
20 by saponification to acid **19** and treatment with thionyl chloride. Acid chloride **20** was usually used without further

purification.

We had first tried to use acid **19** itself as an acylating agent. However, when the acid was treated[31] with cyclohexene or cyclododecene in the presence of polyphosphoric acid at 90 °C we could not detect formation of any acylated material.

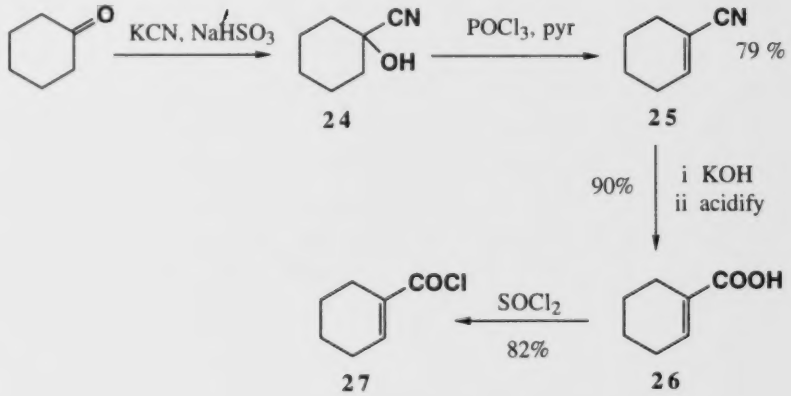
As the acid chloride **20** should be a more reactive species we used it (in the presence of hot PPA or $AlCl_3$[32]) to try to effect acylation of cyclohexene or cyclododecene. However, no identifiable compounds were isolated from the reaction mixtures, and so we next sought to activate the olefin. To this end, 1-trimethylsilylcyclohex-1-ene was prepared from cyclohexanetosylhydrazone via Shapiro reaction. Using Paquette's conditions[13] ($AlCl_3$, CH_2Cl_2, 0 °C) no identifiable products were isolated when the silylated olefin was treated with the acid chloride. We thought that perhaps our acyl substrates were not stable enough to withstand the cyclization conditions, and so we examined the possibility of using stannyl-activated olefins, as described below.

Chong and co-worker[33] reported an easy method for conversion of aldehydes to vinylstannanes and this seemed a good way to make the substrates that we needed. Using Chong's method, aldehyde **21** was converted into vinylstannane **23** (Scheme 20).



Scheme 20

With the vinylstannane in hand, the acid chloride **27** was then prepared as shown in Scheme 21.



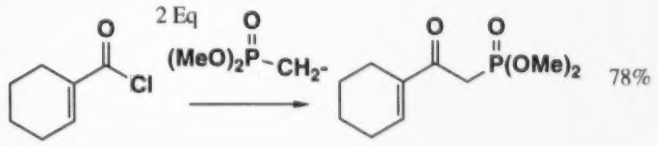
Scheme 21

Treatment of acid chloride **27** with $AlCl_3$, followed by vinylstannane **23**, did not effect acylation and subsequent cyclization; only 5-(phenylseleno)-1-pentene was isolated from the mixture. Recovery of the phenylseleno fragment was encouraging because it indicated that the selenium unit was stable to the reaction conditions. However, when $SnCl_4$ was used as the Lewis acid, no identifiable products were

isolated. A report by Stille showed that acid chlorides and vinyl stannanes could be coupled using a palladium-based reagent,[34] but, when his conditions were tried no reaction took place and most (85%) of the starting vinylstannane **23** was recovered.

II.5. Wadsworth-Horner-Emmons Approach

Acid chloride **27** was converted into the stabilized phosphonate **28** using the methodology of Biller and co-workers[35] as shown in Scheme 22.



27 28

Scheme 22

Formation of phosphonate **28** was encouraging as we felt that a very mild way to generate dienones was at hand. However, alkylation of phosphonate **28** was not observed with 4-(phenylseleno)butanal (**13**) under any of the following conditions:

i) $LiN(SiMe_3)_2$, THF -78 °C to room temperature; then **13**

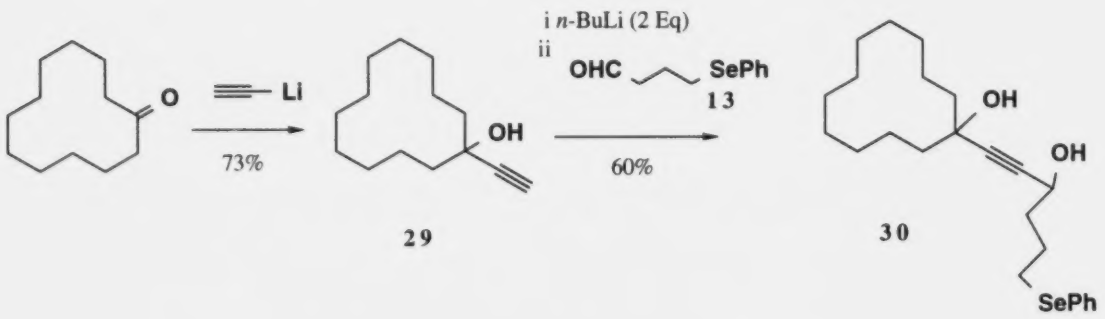
ii) NaH, THF, rt; then **13**

iii) K_2CO_3, MeOH and **13**

In each case a distinct yellow color was present but no dienone was ever formed, and most of the starting aldehyde **13** was usually recovered. To rule out the possibility that aldehyde **13** was resistant to olefination, benzaldehyde was also tried under the above conditions. Again, it was found that no dienone was formed and virtually all of the aldehyde was recovered. We subsequently became aware of a mild procedure for condensing alicyclic phosphonates with aldehydes,[36] but by that stage, we had already recognized that the Nazarov cyclization conditions are incompatible with our substrates containing radical precursors.

II.6. Use of Acetylenic Diols

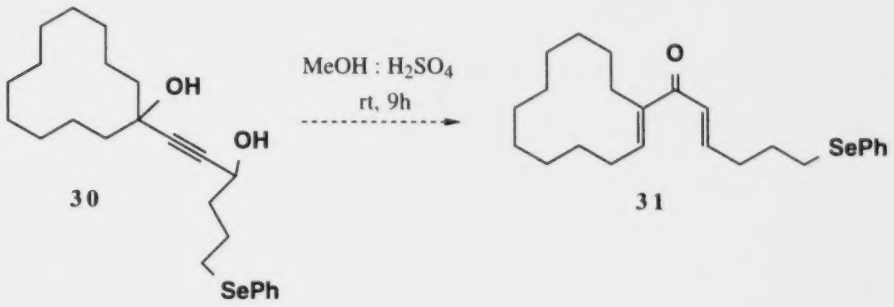
We next turned to the possibility of using acetylenic diols. A suitable substrate (**30**) was easily prepared by the method summarized in Scheme 23.



Scheme 23

Treatment of cyclododecanone with lithium acetylide gave compound **29**, the best results being obtained when Midland's

procedure[37] was followed. Double deprotonation and treatment of the propargylic anion with 4-(phenylseleno)butanal then gave the required diol **30**. The diol was exposed to the following conditions: i) H_2SO_4, MeOH, room temperature; ii) $FeCl_3$;[38,39] formic acid, 90 °C;[40] $MeSO_3H$, room temperature,[15] but no products could be identified. However, treatment with 1:1 MeOH-H_2SO_4 at room temperature[40] did appear to lead to

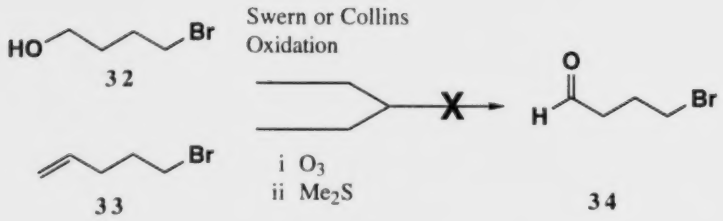


30 31

Scheme 24

some dienone **31** (Scheme 24), since the crude reaction mixture showed IR absorption at 1644 cm^{-1} ($\alpha,\beta,\alpha',\beta'$-dienone carbonyl). Unfortunately, neither the dienone nor the derived cyclized material could be isolated.

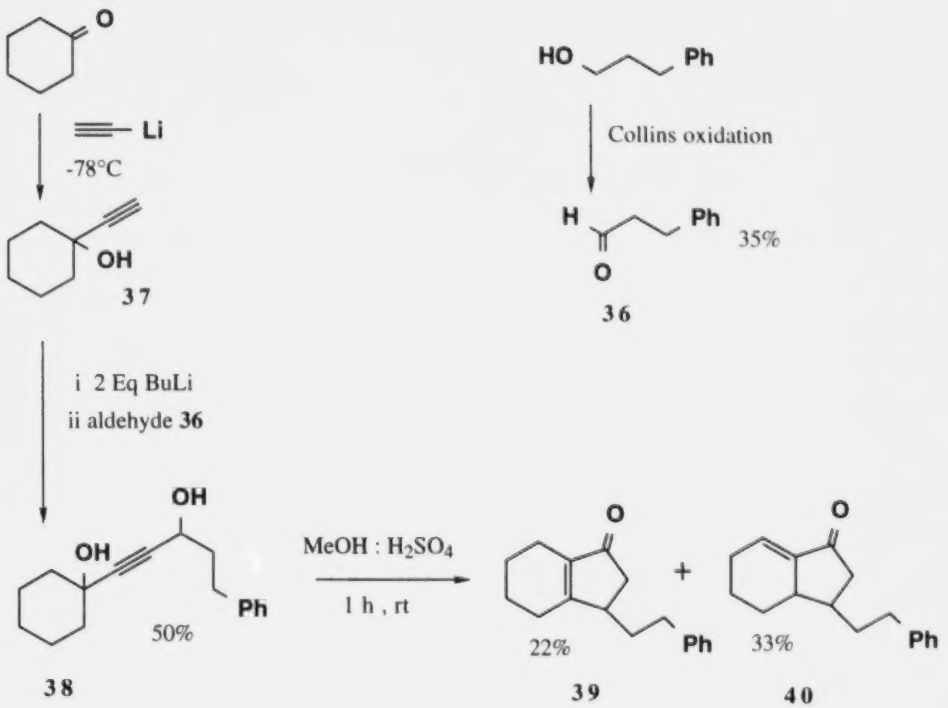
It was felt that the phenylseleno group might be interfering with the Nazarov cyclization. To test for this possibility an attempt was made to prepare some other aldehydes that carried different radical precursors. The most obvious replacement for the phenylseleno group is a bromine atom, and so we tried to prepare 4-bromobutanal (**34**) (Scheme 25).



Scheme 25

When 4-bromobutanol (**32**) was subjected to either Swern or Collins oxidation, the desired product **34** was not isolated. It was felt that ozonolysis of 5-bromo-1-pentene (**33**) would afford an especially mild route to compound **34**. This was indeed the case, and ^1H NMR spectra of the crude reaction mixture indicated that the desired aldehyde **34** was present. However, upon standing for 15 to 30 minutes, **34** decomposed, and the instability of bromoaldehyde **34** forced us to look for alternatives.

There are some examples of compounds containing aromatic rings being used as substrates for the Nazarov reaction,[41,42] and so we felt that the aromatic ring of the phenylseleno group was probably not causing problems. Nevertheless, we decided to run the following control experiment to make certain. The selenium was replaced with a CH_2 group and the experiment was retried, as summarized in Scheme 26.

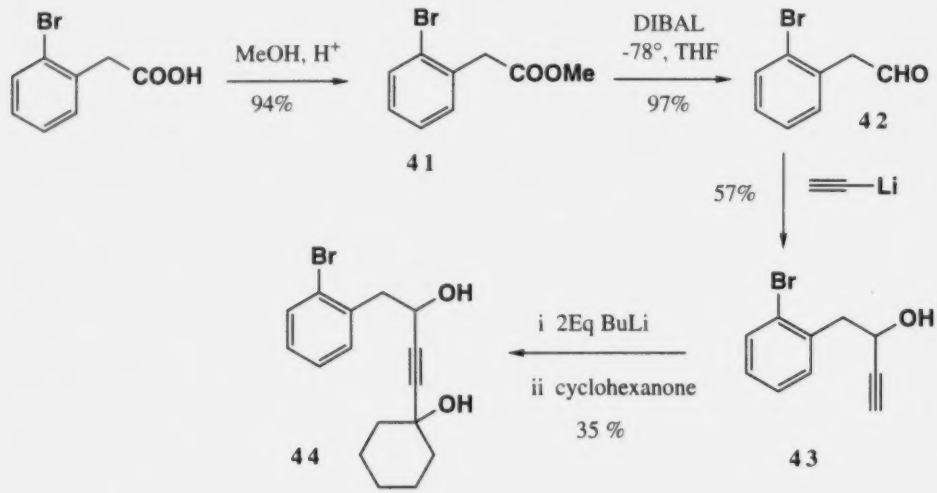


Scheme 26

The required substrate **38** was prepared from cyclohexanone as shown. The alkylation gave a low yield because aldehyde **36** was contaminated with the starting alcohol. However, cyclization to compounds **39** and **40** occurred readily and confirmed our belief that the aromatic ring of the phenylseleno group does not interfere with the required Nazarov process. Consequently, the presence of the selenium functionality in our substrates was the likely reason for the failure of the Nazarov cyclizations.

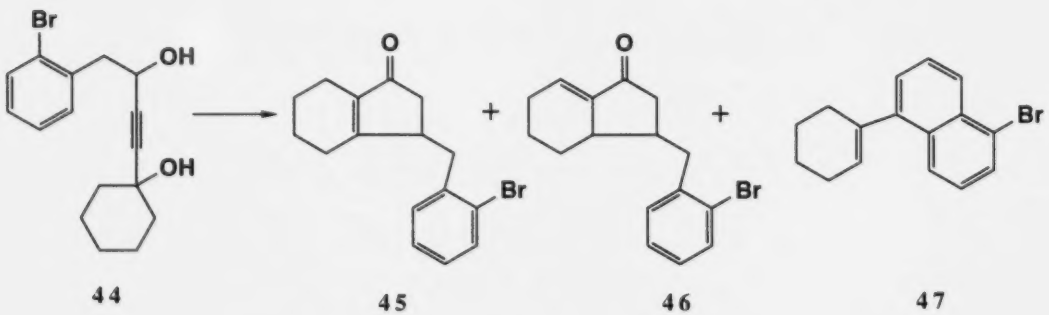
Clearly, a radical source was required other than selenium and it had to survive conditions for the Nazarov process. It was decided to use commercially available 2-(2-

bromophenyl)acetic acid as the starting material in a route (Scheme 27) leading to ynediol **44**, a compound satisfying this requirement.



Scheme 27

Ynediol **44** was easily prepared, and it was subjected to a variety of cyclization conditions. Scheme 28 shows the isolated products, and Table 1 gives the compound ratios and yields of the desired product **45**.



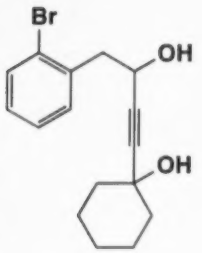
Scheme 28

Table 1: Reaction Conditions and Ratios for Nazarov Cyclization of Compound 44

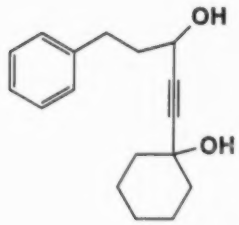
	Yield (%)		
CONDITIONS	**45**	**46**	**47**
MeOH (1):H_2SO_4 (1) (0 °C)	42	0	26
MeOH (1):H_2SO_4 (1) (rt)	32	9	46
MeOH (1):H_2SO_4 (2) (rt)	24	9	33
90% HCOOH (90 °C)	25	0	25
80% HCOOH (90 °C)	18	0	33
$MeSO_3H$ (rt)	3	0	56

The best results were obtained with cold (0 °C) 1:1 MeOH:H_2SO_4, but this result could not be repeated. The rate of addition of the H_2SO_4 is important, and higher yields of the desired compound (**45**) resulted from slow addition of the acid. Reactions using various reagents at higher temperatures gave more of the naphthalene **47**, indicating that carrying out the reaction below 0 °C could be beneficial, but this was not tried.

Formation of naphthalene derivative **47** was unexpected because the aromatic ring had not interfered with other examples reported in the literature or in our previous test experiment.

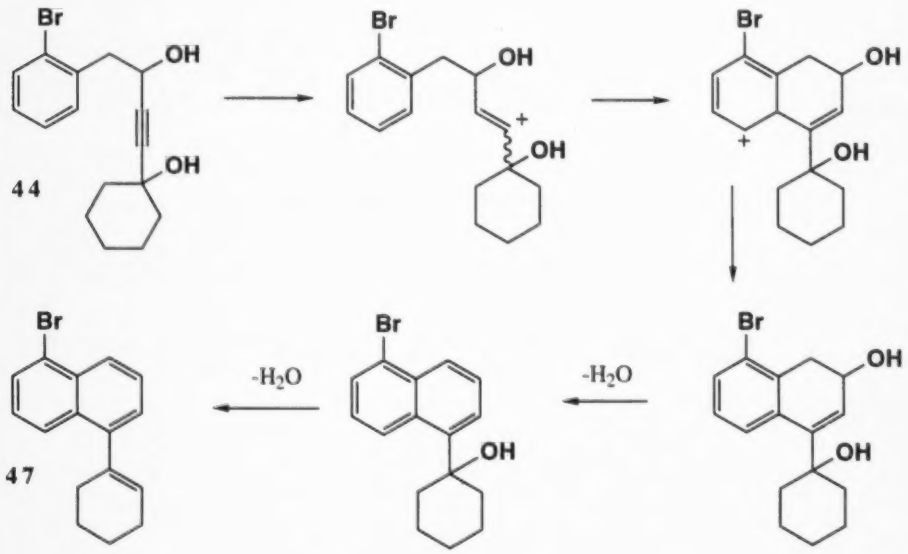


44



38

Examination of compounds **44** and **38** shows one notable difference – there is one less CH_2 in the alkyl chain in compound **44**, thereby placing the aromatic ring in a good position to attack an intermediate carbocation in the reaction pathway and so generate the naphthalene substrate. The following mechanism (Scheme 29) is proposed for formation of bromonaphthalene **47**:



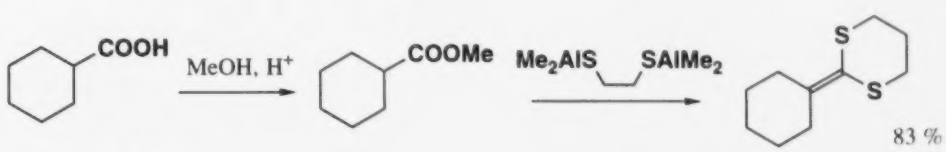
Scheme 29

Although this route did afford the desired substrate

(**45**) for 5-exo radical cyclization, the low yield and a competing side reaction forced us to abandon the method.

II.7. Use of Thioacetal Anions

We decided at this point to try to prepare a carbonyl-protected dienone, and then to develop mild deprotection conditions. A thioacetal appeared to be a suitable protecting group because it would allow generation of an anion at the protected carbonyl carbon, and this anion could then be alkylated. We based our route on the published[43] preparation of compound **48** (Scheme 30).

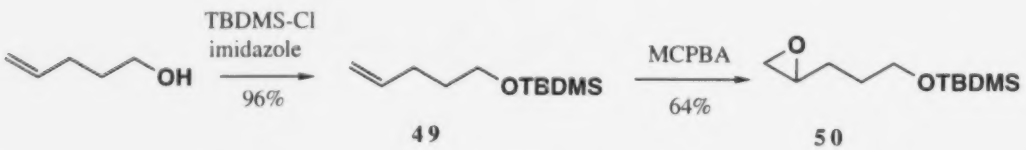


48

Scheme 30

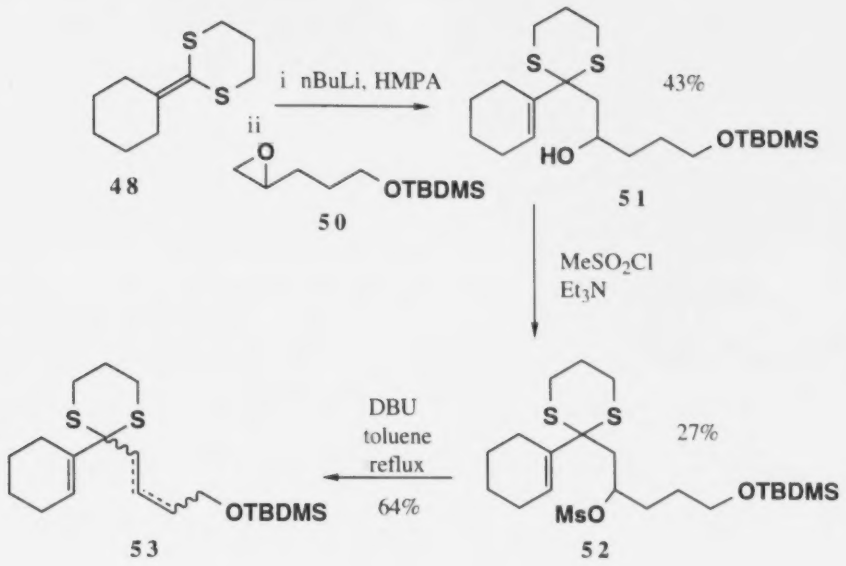
Compound **48** was deprotonated with *n*-BuLi, HMPA was added and then alkylation of the anion was tried with several aldehydes. To our surprise, we did not observe any alkylation and a check of the literature revealed that there were no examples of the anion reacting with aldehydes. All the published examples utilized alkyl halides. Accordingly, we decided to try a terminal epoxide in the hope that reaction would occur at the primary position. Moreover, since it appeared that the phenylseleno group interfered with

the Nazarov reaction, it was thought that a protected alcohol would be the best substrate for the Nazarov process, and that this protected alcohol would eventually be replaced by a homolyzable group. The required epoxide, compound **50**, was prepared as shown in Scheme 31.



Scheme 31

With the anion source and the alkylating agent in hand we tried the reaction and found that it proceeded in the desired manner (Scheme 32), although in low yield, to give **51**. We did not optimize this step, but proceeded directly from alcohol **51** to the corresponding mesylate, compound **52**, which was formed along with some olefinic products (**53**). The mesylate, in turn, was treated with DBU. A mixture of



Scheme 32

alkenes, **53**, was formed, which was unstable to silica gel, but addition of Et_3N did allow isolation of small amounts of the desired products. These compounds were not fully characterized and the structures are based solely on ^1H NMR data. We did try to remove the ketone protecting group using $HgCl_2$, $CaCO_3$ (MeCN:water);[42] $AgNO_3$, AgO (MeCN:water);[44] and isoamyl nitrite (CH_2Cl_2),[45] but all methods were unsuccessful. No identifiable species were isolated from any of the deprotection attempts. Consequently, this route was abandoned.

II.8. Conclusions

Our investigation into the possibility of developing a tandem Nazarov cyclization-5-*exo* radical closure sequence leads us to conclude:

1) The most easily prepared Nazarov substrates are acetylenic diols.
2) The introduction of a phenylseleno group into a Nazarov substrate before cyclization will either hinder or prevent the cyclization.
3) Inclusion of potential nucleophiles (olefins or heteroatoms, for example) in a position either 5 or 6 atoms removed from the location of a potential carbocation in a Nazarov reaction intermediate will probably lead to side products or prevent the Nazarov reaction from taking place.
4) Bromine and ether oxygen atoms[17] appear to be the only heteroatoms that do not interfere with the Nazarov reaction.

III. Experimental

General

Unless otherwise stated, the following procedures apply: Experiments were conducted under a slight static pressure of argon, purified by passage through a column (3.5 x 50 cm) of R-311 deoxygenation catalyst[46] and then through a similar column of Drierite. Glassware was dried in an oven (120 °C) for at least 3 h before use and either assembled quickly, sealed with rubber septa, and allowed to cool under argon or in a desiccator over Drierite. Reaction mixtures were stirred using Teflon-coated magnetic stirring bars.

Products were isolated from solutions by evaporation under water-pump vacuum at, or below, 35 °C, except in the cases of water (55 °C) and pyridine (60 °C). In cases where no further distillation was carried out, the residues were kept under oil pump vacuum (0.1 Torr) and checked for constancy of weight.

Solvents for chromatography and extractions were distilled before use. Commercial thin-layer chromatography (TLC) plates (silica gel, Merck 60F254) were used. Spots were detected by spraying the plate with phosphomolybdic acid,[47] or by dipping the plate in 6 M H_2SO_4 in EtOH followed by charring on a hot plate, or by examination in UV light. All R_f values refer to the chromatographic system which was previously specified in each experimental procedure, unless otherwise stated.

Dry solvents were prepared under argon. Solvents for

reactions were distilled from a suitable drying agent (see below) under argon, and were transferred using cannulas or dry syringes. Dry THF, Et_2O, and dioxane were distilled from sodium and benzophenone ketyl. Dry benzene, toluene, HMPA (vacuum pump, 0.1 Torr) and DMF (vacuum pump, 15 Torr) were distilled from sodium. Dry Et_3N, Et_2NH, CH_2Cl_2, MeOH, $CHCl_3$, DMSO (water-pump vacuum), and pyridine were distilled from CaH_2. Acetone was distilled from anhydrous K_2CO_3. Commercial (Aldrich) solutions of *n*-BuLi, DIBAL, and $LiN(SiMe_3)_2$ were assumed to have the stated molarity.

Melting points were measured on a Kofler block melting point apparatus. FT-IR measurements were made as casts from the specified solvent or as neat films on KBr plates. Only diagnostic peaks have been reported.

Mass spectra were recorded with an AEI Model MS-50 mass spectrometer using an ionizing voltage of 70 eV. Low resolution spectra were recorded with an AEI Model MS-12 (chemical ionization with ammonia) or Model MS-9 (fast atom bombardment) instrument.

Microanalyses were performed by the microanalytical laboratory of this Department.

^1H and ^{13}C NMR spectra were recorded with Bruker WP-80 (^1H at 80 MHz), Bruker WH-200 (^1H at 200 MHz, ^{13}C at 50.3 MHz), Bruker AM-300 (^1H at 300 MHz, ^{13}C at 75.5 MHz), Bruker AM-400 (^1H at 400 MHz, ^{13}C at 100.6 MHz) and Varian Unity 500 (^1H at 500 MHz, ^{13}C at 125.7 MHz) instruments, using the specified deuterated solvent as an internal reference. Some

^{1}H NMR spectra have been treated as first order approximations of second order spin systems. The symbol "ap" has been used to represent the word "apparent" in reporting NMR data.

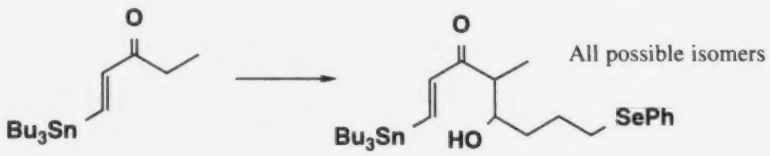
The following is a list of compounds in Part I of this thesis which were prepared using literature methods: *E*-Bis(tributylstannyl)ethene (**10**),[48] 4-(phenylseleno)butanal (**13**),[21] 1-cyanocyclohexan-1-ol (**24**),[49] 1-cyanocyclohexene (**25**),[49] cyclohexenecarboxylic acid (**26**),[50] 1-ethynyl-1-cyclohexanol (**37**),[53] and 2-(cyclohexylidene)-1,3-dithiane (**48**).[43]

(*E*)-1-(Tri-*n*-butylstannyl)-1-penten-3-one (11).

EtCOCl (0.67 mL, 0.71 g, 7.7 mmol) was added to a stirred and cooled (CCl_4/acetone bath, -20 °C) mixture of $AlCl_3$ (4.05 g, 30.4 mmol) and dry CH_2Cl_2 (50 mL) (Ar atmosphere). After 5 min (*Z*)-1,2-bis(tributylstannyl)ethene (**10**) (4.78 g, 7.89 mmol) was added as quickly as possible from a syringe and the mixture was stirred for 1 h. The cooling bath was removed and stirring was continued for 2 h.[51] Hydrochloric acid (2 N, 25 mL) was added. The layers were separated, and the organic phase was dried ($MgSO_4$) and

evaporated to afford **11** (2.83 g, 75%) as a pure (^{1}H NMR, 200 MHz), yellowish oil, which was unstable to chromatography: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84-1.01 (m, 15 H), 1.05-1.14 (m, 3 H), 1.15-1.43 (m, 6 H), 1.45-1.68 (m, 6 H), 2.63 (q, *J* = 7.5 Hz, 2 H), 6.56 (d, *J* = 21 Hz, 1 H), 7.58 (d, *J* = 21 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.13, 9.65, 13.66, 27.24, 28.89, 31.00, 145.45, 149.35, 199.81.

8-(Tri-*n*-butylstannyl)-5-methyl-1-(phenylseleno)-7-octen-6-one-4-ol (12).



n-BuLi (0.61 mL, 1.6 N in hexane, 0.98 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.77 mL, 0.55 g, 0.55 mmol) in dry THF (4 mL) (Ar atmosphere). After 10 min 1-(tributylstannyl)-1-penten-3-one **11** (0.189 g, 0.383 mmol) was added via cannula and the addition flask was rinsed with dry THF (1 mL). 4-(Phenylseleno)butanal **13** (0.148 g, 0.651 mmol) was added via cannula after 20 min and the addition flask was rinsed with dry THF (1 mL). The cooling bath was removed and the mixture was stirred for 1 h. Water (10 mL) was added and the mixture was diluted with CH_2Cl_2 (50 mL) and then washed with 2 N hydrochloric acid (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL).

The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexane, gave impure product. The fractions containing the desired compound were evaporated. Flash chromatography of the new residue over silica gel (1 x 20 cm), using 10% Et_2O-hexane containing 1% Et_3N, gave **12** (15.9 mg, 7%) as a pale yellow oil: R_f = 0.22; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87-0.93 (m, 9 H), 0.97-1.04 (m, 6 H), 1.13-1.16 (m, 3 H), 1.24-1.35 (m, 6 H), 1.47-1.57 (m, 7 H), 1.58-1.68 (m, 1 H), 1.71-1.80 (m, 1 H), 1.90-1.95 (m, 1 H), 2.80-2.30 (m, 3 H), 3.04-3.06 (m, 1 H), 3.89-3.92 (m, 1 H), 6.55 (d, *J* = 17 Hz, 1 H), 7.20-7.28 (m, 3 H), 7.48-7.51 (m, 2 H), 7.67 (d, *J* = 17 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.77, 10.43, 13.65, 26.72, 27.21, 27.79, 28.97, 34.10, 45.71*, 70.45*, 126.71, 129.01, 130.38, 132.49, 144.04, 152.51*, 203.55 (signals denoted with * possess shoulders).

Compound **12** decomposes during chromatography over silica gel.

Ethyl (*E*)-6-(phenylseleno)-2-hexenoate (15).

Triethyl phosphonoacetate (3.00 mL, 3.39 g, 15.1 mmol) was added to LiHMDS (15 mL, 1 N in THF, 15 mmol) (Ar atmosphere), and this solution was then added via cannula,

using a positive pressure of Ar, to a stirred solution of 4-(phenylseleno)butanal (**13**) (2.48 g, 10.9 mmol) in dry THF (20 mL). After 4 h, water (10 mL) was added and the mixture was poured into EtOAc (100 mL). The mixture was washed with 2 N hydrochloric acid (100 mL), saturated aqueous $CuSO_4$ solution (100 mL), and brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 10% EtOAc-hexane, gave **15** (2.38 g, 74%) as an oil: R_f = 0.50; FT-IR ($CHCl_3$ cast) 3025, 1718, 1659, 1135 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28 (t, J = 7.5 Hz, 3 H), 1.80-1.89 (m, 2 H), 2.33 (ddt, J = 7, 7, 2 Hz, 2 H), 2.90 (ap t, J = 7 Hz, 2 H), 4.18 (q, J = 7.5 Hz, 2 H), 5.81 (dt, J = 16, 2 Hz, 1 H), 6.91 (dt, J = 16, 7 Hz, 1 H), 7.20-7.33 (m, 3 H), 7.44-7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.27, 27.08, 28.39, 31.98, 60.20, 122.13, 126.97, 129.08, 129.90, 132.83, 147.65, 166.47; exact mass m/z calcd for $C_{14}H_{18}O_2{}^{80}Se$ 298.0471, found 298.0472. Anal Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10. Found: C, 56.42; H, 6.10.

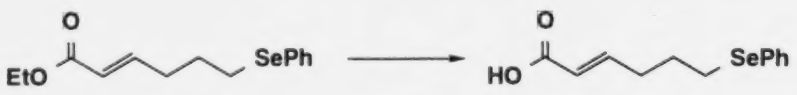
(*E*)-6-Phenylseleno-2-hexenal (16).

i-Bu_2AlH (17 mL, 1 N in CH_2Cl_2, 17 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of the α,β-unsaturated ester **15** (2.38 g, 8.00 mmol) in dry CH_2Cl_2 (50

mL) (Ar atmosphere). After 10 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. Water (10 mL) was added followed by 2 N hydrochloric acid, which was added until the white precipitate dissolved. The mixture was extracted with CH_2Cl_2 (200 mL) and the organic extract was washed with brine (100 mL), dried ($MgSO_4$), and evaporated to afford the expected crude allylic alcohol (^1H NMR, 80 MHz).

DDQ (2.00 g, 8.81 mmol) was added to a solution of the crude alcohol (2.03 g, 7.95 mmol) in dry dioxane (25 mL), and the mixture was refluxed for 1 h, cooled to room temperature, and then filtered through a pad (3 x 5 cm) of flash chromatography grade silica gel. The pad was washed with 20% EtOAc-hexane in 100 mL portions until the washings were free of product (TLC control, silica, 10% EtOAc-hexane). The combined washings were evaporated, and flash chromatography of the residue, using 10% EtOAc-hexane, gave **16** (1.31 g, 64%) as an oil: R_f = 0.19; FT-IR ($CHCl_3$ cast) 3064, 3043, 1689, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.85-1.91 (m, 2 H), 2.48 (ddt, J = 7, 7, 2 Hz, 2 H), 2.92 (ap t, J = 7 Hz, 2 H), 6.10 (ddt, J = 15, 7, 2 Hz, 1 H), 6.79 (dt, J = 15, 7 Hz, 1 H), 7.21-7.32 (m, 3 H), 7.44-7.58 (m, 2 H), 9.49 (d, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.04, 28.20, 32.47, 127.13, 129.10, 129.13, 132.94, 133.47, 157.00, 193.81; exact mass *m/z* calcd for $C_{12}H_{14}O^{80}Se$ 254.0209, found 254.0206. Anal Calcd for $C_{12}H_{14}OSe$: C, 56.92; H, 5.57. Found: C, 56.97; H, 5.59.

(*E*)-6-(Phenylseleno)-2-hexenoic acid (19).



Ester **15** (76.6 mg, 0.257 mmol) was dissolved in 5:1 MeOH:water (6 mL) and K_2CO_3 (343 mg, 2.47 mmol) was added. The mixture was stirred at room temperature for 1 h (TLC control, silica, 10% EtOAc-hexane). No reaction was observed. The mixture was then heated at 80 °C for 24 h, cooled, poured into CH_2Cl_2 (25 mL), and extracted with 2 N NaOH (2 x 10 mL). The basic aqueous extract was washed with CH_2Cl_2 (2 x 25 mL) and then acidified (concentrated hydrochloric acid) to pH 1 (indicator paper). The aqueous mixture was extracted with CH_2Cl_2 (2 x 25 mL). The extract was dried ($MgSO_4$) and evaporated to afford acid **19** (68.3 mg, 98%) as an oil: FT-IR ($CHCl_3$ cast) 3400-2700, 1693, 1648, 1420 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.83-1.94 (m, 2 H), 2.37 (ddt, J = 7, 7, 2 Hz, 2 H), 2.91 (ap t, J = 7 Hz, 2 H), 5.81 (br d, J = 15 Hz, 1 H), 7.02 (dt, J = 15, 7 Hz, 1 H), 7.21-7.32 (m, 3 H), 7.45-7.53 (m, 2 H), (the carboxylic acid proton was not observed); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.1, 28.4, 32.1, 121.4, 127.7, 129.1, 129.9, 133.0, 150.6, 171.7; exact mass *m/z* calcd for $C_{12}H_{14}O_2{}^{80}Se$ 270.0158, found 270.0162. Anal Calcd for $C_{12}H_{14}O_2Se$: C, 53.54; H, 5.24. Found: C, 53.40; H, 5.08.

(*E*)-6-(Phenylseleno)-2-hexenoyl chloride (20).

$SOCl_2$ (45 μL, 73 mg, 0.62 mmol) was added to a stirred solution of acid **19** (81.0 mg, 0.301 mmol) in dry benzene (3 mL) (Ar atmosphere). The mixture was refluxed for 1.5 h and then cooled to room temperature. The solvent was evaporated, and Kugelrohr distillation (oven temperature 130 °C, 0.6 Torr) of the residue gave **20** (48.3 mg, 56%): FT-IR ($CHCl_3$ cast) 1759, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.89 (m, 2 H), 2.43 (ddt, *J* = 7, 7, 2 Hz, 2 H), 2.91 (ap t, *J* = 7 Hz, 2 H), 6.05 (dt, *J* = 15, 2 Hz, 1 H), 7.15 (dt, *J* = 15, 7 Hz, 1 H), 7.20-7.35 (m, 3 H), 7.43-7.52 (m, 2 H); exact mass *m/z* calcd for $C_{12}H_{13}ClOSe$ 287.9819, found 287.9815. The product was used promptly.

Tributyl[1-iodo-5-(phenylseleno)pentyl]stannane (22).

n-BuLi (3.45 mL, 1.6 N in hexane, 5.5 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.78 mL, 0.56 g, 5.5 mmol) in dry THF (10 mL) (Ar atmosphere). After 10 min, the mixture was cooled to -78 °C (dry ice-acetone bath) and Bu_3SnH (1.45 mL, 1.57 g, 5.4 mmol) was added.

Stirring was continued for 20 min, compound **21**[52] (1.29 g, 5.36 mmol) was added, the cold bath was removed, and the mixture was stirred for 1 h while it attained room temperature. Saturated aqueous NH_4Cl (5 mL) and EtOAc (50 mL) were added and the organic phase was washed with saturated aqueous NH_4Cl (30 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated.

Ph_3P (2.14 g, 8.16 mmol), imidazole (2.10 g, 8.26 mmol), and I_2 (2.09 g, 8.25 mmol) were added to a stirred and cooled (0 °C) solution of the resulting crude alcohol in THF (8 mL). After 5 min, the cold bath was removed and stirring at room temperature was continued for 2 h. The reaction mixture was poured into hexane (30 mL) and washed with acetonitrile (15 mL) to remove the iodine. The hexane layer was evaporated, and flash chromatography of the residue over silica gel (5 x 20 cm), using 2% EtOAc-hexane, gave **22** (3.01 g, 49%) as an oil: R_f = 0.44; FT-IR ($CHCl_3$ cast) 3070, 3056, 3031 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.70-1.10 (m, 15 H), 1.10-2.00 (m, 18 H), 2.87 (ap t, J = 7 Hz, 2 H), 3.25-3.31 (m, 1 H), 7.10-7.28 (m, 3 H), 7.32-7.45 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.7, 12.0, 13.2, 16.5, 27.3, 28.9, 29.2, 32.5, 37.4, 126.7, 129.0, 132.7, 143.5; mass (CI) m/z calcd for $C_{23}H_{41}{}^{127}I^{80}Se^{120}Sn$ 644, found 662 (M + 18).

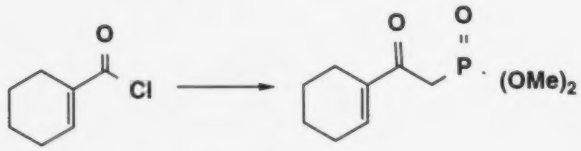
Tributyl[5-(phenylseleno)-1-penten-1-yl]stannane (23).

DBU (1.10 mL, 1.12 g, 7.35 mmol) was added to a stirred solution of compound **22** (1.53 g, 2.43 mmol) in dry THF (20 mL) (Ar atmosphere). The mixture was refluxed for 16 h and then cooled to room temperature. Et_2O (50 mL) was added and the mixture was washed with 2 N hydrochloric acid (2 x 30 mL), and brine (50 mL), dried ($MgSO_4$), and evaporated to afford crude **23** (0.846 g, 69%), which was not further purified because of its instability to heat and chromatography (2D TLC, silica gel, hexane). The crude material appeared pure by ^1H NMR and ^{13}C NMR and had: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.70-1.10 (m, 15 H), 1.15-1.81 (m, 14 H), 2.10-2.32 (m, 2 H), 2.88 (ap t, J = 7 Hz, 2 H), 5.87-5.94 (m, 1 H), 7.13-7.24 (m, 4 H), 7.47-7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) (major isomer only) δ 9.4, 13.6, 27.3, 29.1, 29.3, 37.7, 126.6, 128.7, 128.9 (two coincident peaks), 132.5 (two coincident peaks), 147.9.

1-Cyclohexenecarbonyl chloride (27).

$SOCl_2$ (11.0 mL, 17.9 g, 151 mmol) was added to a stirred solution of 1-cyclohexenecarboxylic acid (**26**) (9.01 g, 71.2 mmol) in dry benzene (40 mL) (Ar atmosphere). The mixture was refluxed for 1 h, and then the benzene and excess of $SOCl_2$ were removed by vacuum distillation. Distillation of the residue afforded 1-cyclohexenecarbonyl chloride (**27**) (8.46 g, 82%): bp 110-112 °C, 16 Torr; FT-IR ($CHCl_3$ cast) 3060, 1750, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.58-1.72 (m, 4 H), 2.26-2.42 (m, 4 H), 7.40-7.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.9, 21.8, 25.2, 28.7, 135.0, 150.3, 168.2; exact mass *m/z* calcd for C_7H_9ClO 144.0342, found 144.0345.

Dimethyl 2-(1-Cyclohexenyl)-2-oxoethylphosphonate (28).



n-BuLi (75.00 mL, 1.6 N in hexane, 0.12 mol) was added to a stirred and cooled (-78 °C) solution of dimethyl methylphosphonate (13.0 mL, 14.9 g, 0.12 mol) in THF (75 mL). After 1 h the reaction mixture appeared milky and 1-cyclohexenecarbonyl chloride (**27**) (6.45 g, 44.6 mmol) was added, producing a yellow solution. Stirring was continued for 2 h, and then the cooling bath was removed so that the mixture attained room temperature. Saturated aqueous NH_4Cl and then

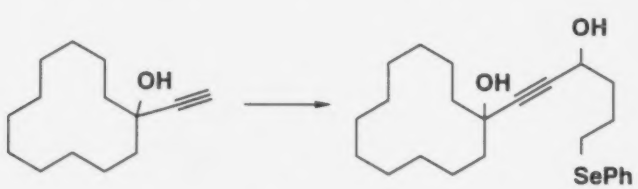
2 N hydrochloric acid were added until the yellow color was discharged. Brine (150 mL) and EtOAc (150 mL) were added and the solution was extracted with EtOAc (5 x 75 mL). The combined organic extracts were washed with brine (2 x 150 mL), and dried ($MgSO_4$). The solution was filtered through a pad of flash chromatography grade silica (5 cm), using first 40% EtOAc-hexane (300 mL) and then EtOAc (1 L). The EtOAc wash was evaporated to give pure [^{1}H NMR, 500 MHz] **28** (8.10 g, 78%) as an oil: FT-IR ($CHCl_3$ cast) 1661, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58-1.72 (m, 4 H), 2.20-2.38 (m, 4 H), 3.35 (d, $^2J_{PH}$ = 22 Hz, 2 H), 3.79 (d, $^3J_{PH}$ = 11 Hz, 6 H), 7.01 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.3, 21.7, 23.0, 26.3, 36.0 (d, $^1J_{PC}$ = 135 Hz, C-2), 53.0 (d, $^2J_{PC}$ = 6 Hz, OCH_3), 127.4, 143.7, 192.5; exact mass *m/z* calcd for $C_{10}H_{17}O_4P$ 232.0864, found 232.0864.

1-Ethynyl-1-cyclododecanol (29).

This compound has been reported before,[54] but was now prepared by a different procedure, as follows. Acetylene was bubbled through a stirred and cooled (0 °C) solution of *n*-BuLi (8.00 mL, 1.6 N in hexane, 13 mmol) in dry THF (25 mL) for *ca.* 40 min. Cyclododecanone (2.02 g, 11.1 mmol) was

added slowly, producing a pale yellow solution, which was stirred for 3 h. Saturated aqueous NH_4Cl (10 mL) was added and the resulting mixture was poured into saturated aqueous NH_4Cl (50 mL) and brine (50 mL). The mixture was extracted with CH_2Cl_2 (4 x 75 mL) and the combined organic extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 10% EtOAc-hexane, gave **29** [0.645 g, 73%, corrected for recovered cyclododecanone (1.25 g)] as an oil: FT-IR ($CHCl_3$ cast) 3600-3200, 3275, 3240, 1123 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.37 (br s, 16 H), 1.50-2.00 (m, 7 H), 2.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.8, 22.4, 16.0, 26.2, 36.1, 71.4, 86.7, 88.0; exact mass *m/z* calcd for $C_{14}H_{24}O$ 208.1827, found 208.1819. Anal Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.86; H, 12.04.

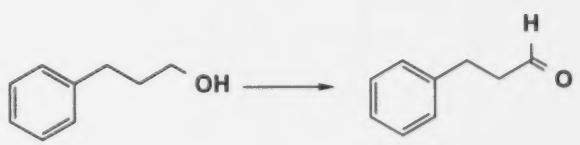
1-[3-Hydroxy-6-(phenylseleno)-1-hexynyl]-1-cyclododecanol (30).



n-BuLi (1.95 mL, 1.6 N in hexane, 3.1 mmol) was added to a stirred and cooled (-78 °C) solution of 1-ethynylcyclododecan-1-ol (**29**) (0.329 g, 1.55 mmol) in dry THF (6 mL) (Ar

atmosphere). A solution of 4-(phenylseleno)butanal (**13**) (0.348 g, 1.53 mmol) in dry THF (1 mL) was then added via cannula. After 15 min the cold bath was removed and the reaction mixture was allowed to warm to room temperature. Water (10 mL) was added and the mixture was poured into brine (150 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 40% EtOAc-hexane, gave **30** (0.410 g, 60%) as an oil, contaminated with < 5 mol% EtOAc (^1H NMR, 200 MHz): R_f = 0.44; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40-1.95 (m, 24 H), 2.67 (s, 2 H), 2.93 (ap t, J = 6 Hz, 2 H), 3.02 (d, J = 6 Hz, 2 H), 4.35-4.42 (m, 1 H), 7.19-7.30 (m, 3 H), 7.43-7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz, mixture of diastereoisomers) δ 19.6, 22.2, 22.5, 25.9, 26.0, 17.5, 35.7, 37.6, 61.5, 61.8, 70.7, 85.2, 89.6, 126.7, 129.0, 130.3, 132.5.

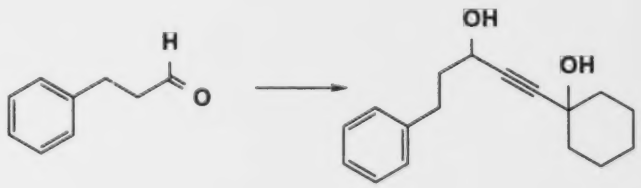
3-Phenylpropanal (36).



This compound has previously been prepared using different procedures.[55] AcONa (10.00 g, 122 mmol), crushed 4Å molecular sieves (11.00 g), and pyridinium chlorochromate (10.78 g, 50.0 mmol) were added to stirred and cooled (0 °C)

dry CH_2Cl_2 (100 mL) (Ar atmosphere). A solution of 3-phenylpropanol (5.60 mL, 5.46 g, 40 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1.5 h. The mixture was stirred for an additional 30 min, at which time little starting material remained (TLC control, silica, 10% EtOAc-hexane). The mixture was filtered twice through a pad (2 x 8 cm) of Celite and the filtrate was evaporated. Flash chromatography of the residue over silica gel (6 x 20 cm), using 10% EtOAc-hexane, gave crude **36** [2.51 g, 35%, containing *ca.* 30 mol % of unreacted starting material (^{1}H NMR, 200 MHz)]. The crude material had: FT-IR ($CHCl_3$ cast) 3031, 3028, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.83 (m, 2 H), 3.04 (ap t, J = 7 Hz, 2 H), 7.20-7.43 (m, 5 H), 9.86 (t, J = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.04, 45.13, 126.22, 128.34, 128.48, 140.30, 201.49; exact mass *m/z* calcd for $C_9H_{10}O$ 134.0732, found 134.0731. The material was used directly for the next step without purification.

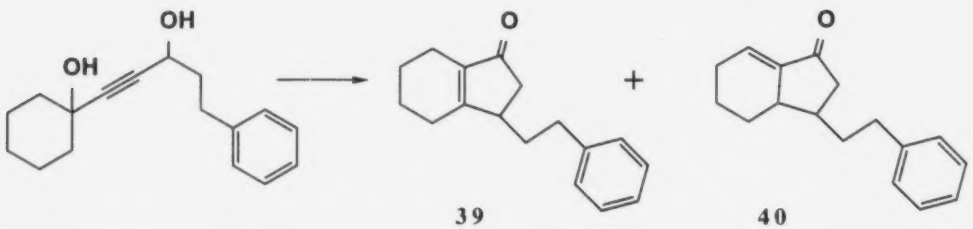
1-(3-Hydroxy-5-phenyl-1-pentynyl)-1-cyclohexanol (38).



n-BuLi (1.60 mL, 1.6 N in hexane, 2.6 mmol) was added to a stirred and cooled (-78 °C) solution of 1-ethynyl-1-

cyclohexanol (**37**) (176 mg, 1.42 mmol) in dry THF (10 mL) (Ar atmosphere). After 10 min, the cold bath was removed and the reaction mixture was allowed to attain room temperature. A solution of aldehyde **36** [contaminated with *ca.* 30 mol % the corresponding alcohol (^{1}H NMR, 200 MHz)] (187 mg, 1.39 mmol) in THF (2 mL plus 2 x 1.5 mL as rinses) was added and the mixture was stirred for 20 min. Hydrochloric acid (2 N, 3 mL) was added and the mixture was poured into brine (100 mL), and extracted with CH_2Cl_2 (4 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 40% EtOAc-hexane, gave diol **38** (182 mg, 50%): R_f = 0.23; FT-IR ($CHCl_3$ cast) 3400-3100, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.14-1.78 (m, 8 H), 1.82-2.18 (m, 6 H), 2.80 (ap t, J = 7 Hz, 2 H), 4.42 (ap t, J = 7 Hz, 1 H), 7.14-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.37 (two coincident peaks), 25.17, 31.53, 39.42, 39.95 (two coincident peaks), 61.81, 68.68, 85.06, 89.04, 126.05, 128.53 (two coincident peaks), 141.33; exact mass *m/z* calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1618.

2,3,4,5,6,7-Hexahydro-3-(2-phenylethyl)-(1*H*)-inden-1-one (39) and 2,3,3a,4,5,6-Hexahydro-3-(2-phenylethyl)-(1*H*)-inden-1-one (40).



39 40

Diol **38** (74.5 mg, 0.288 mmol) was dissolved in dry MeOH (3 mL) and then concentrated H_2SO_4 (3 mL) was added dropwise, creating a purple solution which then turned brown. The solution was stirred and, after 60 min (TLC control, silica, 15% EtOAc-hexane), brine (15 mL) was added. The mixture was extracted with Et_2O (2 x 25 mL) and the combined organic extracts were washed with brine (2 x 25 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 15% EtOAc-hexane, gave two isomers, **39** (15.1 mg, 22%) and **40** (23.0 mg, 33%). Compound **39** had: R_f = 0.65; FT-IR ($CHCl_3$ cast) 3025, 1696, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05-1.75 (m, 5 H), 1.91-2.18 (m, 4 H), 2.19-2.39 (m, 2 H), 2.40-2.68 (m, 4 H), 7.03-7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.0, 21.7, 22.2, 26.5, 33.6, 34.7, 41.0, 41.5, 126.1, 128.4, 128.5, 138.8, 141.6, 176.0, 208.0; exact mass *m/z* calcd for $C_{17}H_{20}O$ 240.1514, found 240.1516.

Compound **40** had: R_f = 0.23; FT-IR ($CHCl_3$ cast) 1673,

1642 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05-1.96 (m, 9 H), 2.35-2.47 (m, 2 H), 2.76 (ap t, *J* = 8 Hz, 2 H), 2.97 (ddt, *J* = 11, 11, 5 Hz, 1 H), 6.72 (ap t, *J* = 5 Hz, 1 H), 7.05-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.44, 25.85, 25.99, 27.61, 29.14, 29.75, 47.59, 125.97, 126.57, 127.68, 128.42, 134.42, 136.40, 139.52, 206.64; exact mass *m/z* calcd for $C_{17}H_{20}O$ 240.1514, found 240.1514.

Methyl 2-(2-Bromophenyl)ethanoate (41).

2-(2-Bromophenyl)acetic acid (2.50 g, 11.6 mmol) was dissolved in MeOH (50 mL) and concentrated H_2SO_4 (1 drop) was added. The solution was refluxed overnight and then cooled to room temperature. The excess of MeOH was evaporated and the residual oil was dissolved in CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL), and dried ($MgSO_4$). Evaporation of the solvent afforded methyl 2-(2-bromophenyl)ethanoate (**41**) (2.55 g, 94%) as an oil: FT-IR ($CHCl_3$ cast) 3071, 1760, 1571, 1470, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 3 H), 3.84 (s, 2 H), 7.10-7.25 (m, 1 H), 7.25-7.37 (m, 2 H), 7.57 (br d, *J* = 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.34, 51.99, 124.87, 127.42, 128.75, 131.33, 132.67, 134.07, 170.76; exact mass *m/z* calcd for

$C_9H_9{}^{79}BrO_2$ 227.9786, found 227.9787. Anal Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96; Br, 34.88. Found: C, 47.29; H, 3.91; Br, 34.95.

2-(2-Bromophenyl)ethanal (42).

i-Bu_2AlH (9.50 mL, 1.0 N in CH_2Cl_2, 9.5 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of methyl 2-(2-bromophenyl)ethanoate (**41**) (2.17 g, 9.47 mmol) in dry CH_2Cl_2 (50 mL) (Ar atmosphere). After 20 min, water (10 mL) was added and the mixture was allowed to attain room temperature, with the cold bath left in place, but not recharged. Hydrochloric acid (2 N) was added until the precipitate dissolved and then the layers were separated. The organic phase was washed with brine (3 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (8 x 20 cm), using 5% EtOAc-hexane, gave 2-(2-bromophenyl)ethanal (**42**) (1.83 g, 97%): R_f = 0.22; FT-IR ($CHCl_3$ cast) 1736, 1585, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.88 (d, J = 2 Hz, 2 H), 7.15-7.40 (m, 3 H), 7.66 (dd, J = 8, 2 Hz, 1 H), 9.79 (t, J = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 49.9, 124.4, 127.3, 128.7, 131.1, 132.1, 132.5, 197.5; exact mass *m/z* calcd for $C_8H_7{}^{79}BrO$ 197.9680, found 197.9665. Anal

Calcd for $C_8H_7BrO_2$: C, 48.27; H, 3.54; Br, 40.14. Found: C, 48.16; H, 3.51.; Br, 39.83

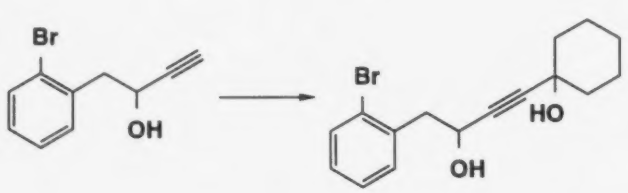
1-(2-Bromophenyl)-3-butyn-2-ol (43).

Dry THF (100 mL) was placed in a flask fitted with a low temperature thermometer (Ar atmosphere) and the level was marked on the outside. THF (30 mL) was removed by syringe and the flask was placed in a dry ice-acetone bath. Acetylene was bubbled through the THF until the level returned to the mark. During this time *n*-BuLi (10 mL, 1.6 N in hexane, 16 mmol) was added to cold (-78 °C) THF (10 mL) and the resulting solution was added over 30 min to the THF-acetylene mixture via cannula, using a positive pressure of Ar. Slow addition is essential as the temperature must not exceed -70 °C and should be closely monitored. The cloudy mixture resulting from this addition* was stirred for 15 min. A cooled (-78 °C) solution of aldehyde **42** (1.36 g, 6.86 mmol) in dry THF (10 mL) was added dropwise to the lithium acetylide solution via cannula, and stirring was continued for 30 min. The cold bath was then removed. After 30 min

*The rapid addition of *n*-BuLi causes production of lithium carbide, the white precipitate and source of the cloudiness. This precipitation is very undesirable, and leads to low yields.

water (50 mL) was added cautiously (acetylene evolution) and then the mixture was poured into hexane (100 mL). Hydrochloric acid (2 N) was added until the yellow color disappeared. The organic phase was washed with 2 N hydrochloric acid (50 mL), water (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 10% EtOAc-hexane, gave some aldehyde (0.150 g, 6.10 mmol) and the desired product **43** (0.885 g, 57%, 64% corrected for recovered aldehyde) as a yellowish solid: R_f = 0.12; mp 64-65 °C (from hexane); FT-IR ($CHCl_3$ cast) 3600-3200, 3294 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.35-2.46 (br s, 1 H), 2.49 (d, *J* = 3 Hz, 1 H), 3.17 (d, *J* = 8 Hz, 2 H), 4.68 (ddd, *J* = 8, 8, 3 Hz, 1 H), 7.03-7.34 (m, 3 H), 7.53 (dd, *J* = 9, 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.11, 61.66, 73.92, 83.53, 124.94, 127.41, 128.75, 132.26, 132.92, 136.06; exact mass *m/z* calcd for $C_{10}H_8{}^{79}BrO$ (M - H) 222.9780, found 222.9759.

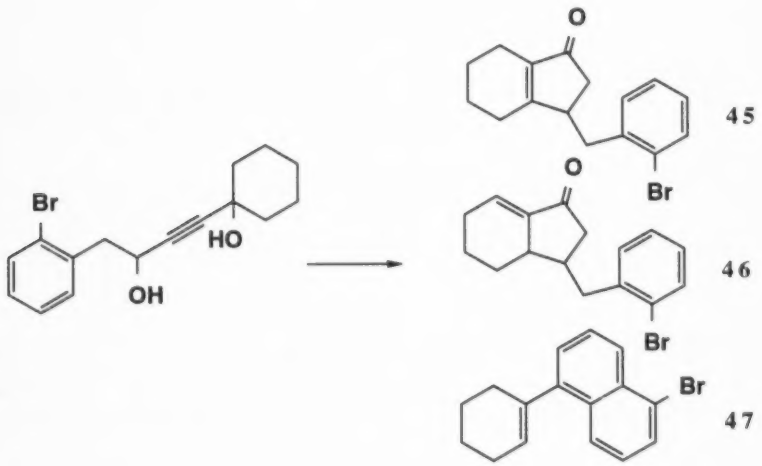
1-[4-(2-Bromophenyl)-3-hydroxy-1-butynyl]-1-cyclohexanol (44).



n-BuLi (0.90 mL, 1.6 N in hexane, 1.4 mmol) was added to

a stirred and cooled (-78°) solution of alcohol **43** (96.0 mg, 0.427 mmol) in dry THF (6 mL) (Ar atmosphere). After 5 min the cold bath was removed for *ca.* 5 min and then replaced. Freshly distilled cyclohexanone (75 μL, 70 mg, 0.71 mmol) was added and, after 5 min, the bath was removed and stirring was continued for 30 min. The reaction mixture was poured into a separatory funnel and 2 N hydrochloric acid was added until no yellow color remained. The aqueous phase was extracted with Et_2O (3 x 25 mL) and the combined organic extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 40% EtOAc-hexane, gave **44** (47.9 mg, 35%) as an oil: R_f = 0.24; FT-IR ($CHCl_3$ cast) 3600-3200, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.80-1.28 (m, 2 H), 1.28-1.86 (m, 10 H), 3.07-3.16 (m, 2 H), 4.68 (ap t, *J* = 8 Hz, 1 H), 6.85-7.32 (m, 3 H), 7.44 (dd, *J* = 9, 2 Hz, 1 H); exact mass *m/z* calcd for $C_{16}H_{19}{}^{79}BrO_2$ 322.0569, found 322.0566.

General procedures for attempted Nazarov reactions leading to: 2,3,4,5,6,7-Hexahydro-3-(2-bromophenylmethyl)-(1*H*)-inden-1-one (45); 2,3,3a,4,5,6-Hexahydro-3-(2-bromophenylmethyl)-(1*H*)-inden-1-one (46); 1-Bromo-5-(1-cyclohexen-1-yl)naphthalene (47).



Method A:

Concentrated H_2SO_4 (3.0 mL) was added dropwise (exothermic reaction) to a stirred solution of diol **44** (69.0 mg, 0.207 mmol) in bench MeOH (3.0 mL), affording a purple solution. Stirring was continued for 2.5 h, at which point no starting material remained (TLC control, silica, 5% EtOAc-hexane). The mixture was poured into water (50 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 5% EtOAc-hexane, gave **47** (16.4

mg, 26%): R_f = 0.80 (in 15% EtOAc-hexane, silica); FT-IR ($CHCl_3$ cast) 3031, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.71-1.96 (m, 4 H), 2.22-2.44 (m, 4 H), 5.77 (m, 1 H), 7.27-7.38 (m, 2 H), 7.54 (dd, *J* = 9, 7 Hz, 1 H), 7.79 (dd, *J* = 7, 2 Hz, 1 H), 8.01 (ddd, *J* = 9, 9, 2 Hz, 1 H), 8.19 (ddd, *J* = 9, 9, 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.25, 23.22, 25.57, 31.23, 123.21, 125.75, 125.84, 125.91, 126.89, 127.84, 128.83, 129.73, 132.29, 132.88, 137.50, 143.62; exact mass *m/z* calcd for $C_{16}H_{15}{}^{79}Br$ 286.0357, found 286.0339.

Further development with 15% EtOAc hexane gave **45** (27.0 mg, 42%) as a pure (^1H NMR, 200 MHz) oil: R_f = 0.17; FT-IR (CH_2Cl_2 cast) 1697, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40-2.00 (m, 5 H), 2.08-2.66 (m, 6 H), 3.11-3.19 (m, 1 H), 3.36 (dd, *J* = 12, 5 Hz, 1 H), 7.08-7.34 (m, 3 H), 7.58 (d, *J* = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.07, 21.68, 22.25, 26.53, 39.96, 40.73, 41.82, 124.62, 127.58, 128.27, 130.82, 133.14, 139.20 (2 coincident peaks), 175.40, 207.54; exact mass *m/z* calcd for $C_{16}H_{17}{}^{79}BrO$ 304.0463, found 304.0448.

Method B:

Concentrated H_2SO_4 (2.0 mL) was added dropwise over 5 min to a stirred and cooled (0 °C) solution of diol **44** (70.0 mg, 0.207 mmol) in bench MeOH (1.0 mL), to afford a pink solution which gradually turned purple. The cold bath was removed after 30 min, and stirring was continued for 1.5 h, at which point no starting material remained (TLC control, silica, 15% EtOAc-hexane). Et_2O (10 mL) was added and the

mixture was poured into brine (25 mL) and extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 15% EtOAc-hexane, gave **47** (27.4 mg, 46%) (R_f = 0.89). A second product, tentatively assigned as compound **46**, (4.2 mg, *ca.* 9%) was then eluted: R_f = 0.34; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.77 (dd, J = 13, 8 Hz, 1 H), 3.22 (dd, J = 13, 4 Hz, 1 H), 6.68 (m, 1 H), 7.09 (m, 1 H), 7.13-7.35 (m, 2 H), 7.53 (dd, J = 8, 1 Hz, 1 H). The ^1H NMR data are consistent with structure **46**; however, the material was not pure and so definitive assignment was not possible. The desired compound **45** (14.8 mg, 32%) was eluted last (R_f = 0.17 in the 15% EtOAc-hexane solvent system). Compounds **45** and **47** had ^1H NMR spectra identical to those of material made by method A.

Method C:

A solution of diol **44** (49.6 mg, 155 mmol) in MeOH (2 mL) was added dropwise with stirring to concentrated H_2SO_4 (4.0 mL) over 2 min. A purple color formed gradually. The mixture was stirred for 1.5 h and then poured into a separatory funnel. Brine (50 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (2 x 25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 15% EtOAc-hexane, gave three products:

47 (15.0 mg, 33%), **46** (3.9 mg, 9%) and **45** (11.4 mg, 24%). The ^{1}H NMR spectra of these compounds were identical to those obtained previously.

Method D:

Diol **44** (26.3 mg, 81 μmol) was dissolved in 90% formic acid (7.5 mL) and the solution was stirred and heated at 90 °C for 22 h. A purple color developed after 2 h. The mixture was cooled to room temperature, poured into Et_2O (100 mL), and washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 20 cm), using 15% EtOAc-hexane, gave **45** (6.2 mg, 25%) and **47** (6.0 mg, 25%). The ^{1}H NMR spectra for these compounds were identical to those obtained previously.

Method E:

A stirred solution of diol **44** (52.6 mg, 163 μmol) in 80% formic acid (4.0 mL) was refluxed for 48 h, cooled to room temperature, and poured into a separatory funnel. Water (30 mL) was added and the mixture was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (0.5 x 20 cm), using 15% EtOAc-hexane, gave **45** (8.9 mg, 18%) and **47** (15.5 mg, 33%). The ^{1}H NMR spectra for these compounds were identical to those

obtained previously.

Method F:

Diol **44** (40.0 mg, 124 μmol) was dissolved in $MeSO_3H$ (5.0 mL), affording a purple solution, which was stirred for 6 h. The mixture was poured into a separatory funnel and brine (50 mL) was added. The mixture was extracted with Et_2O (3 x 25 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (0.5 x 20 cm), using 15% EtOAc-hexane, gave **45** (1.2 mg, 3%) and **47** (20.1 mg, 56%). The ^1H NMR spectra for these compounds were identical to those obtained previously.

(1,1-Dimethylethyl)dimethyl[(4-penten-1-yl)oxy]silane (49).

This compound has been reported previously several times; however, no experimental details or data were given.[56] 4-Penten-1-ol (2.00 mL, 1.67 g, 19.3 mmol) was added to a stirred mixture of TBDMSCl (3.02 g, 20.0 mmol) and imidazole (1.42 g, 20.9 mmol) in dry CH_2Cl_2 (25 mL) and stirring was continued for 4 h. The mixture was poured into 2 N hydrochloric acid (30 mL), and the organic phase was washed

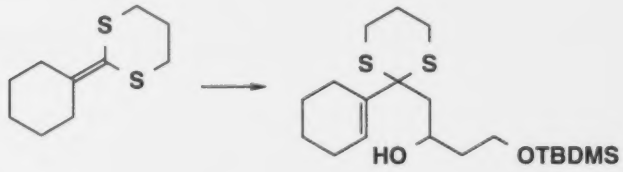
with brine (30 mL), dried ($MgSO_4$), and evaporated, affording ether **49** (3.73 g, 96%): FT-IR ($CHCl_3$ cast) 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.61 (m, 2 H), 2.11 (ap q, *J* = 7 Hz, 2 H), 3.62 (ap t, *J* = 7 Hz, 2 H), 4.90-5.10 (m, 2 H), 5.82-5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -5.31, 18.32, 25.95, 30.03, 32.04, 62.52, 114.45, 138.55; mass (FAB) *m/z* calcd for $C_{11}H_{25}OSi$ (M + H) 201, found 201.

2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-oxirane (50).

This compound has been reported previously, but no experimental details or data were given.[57] A solution of *m*-chloroperbenzoic acid (*ca.* 50-60% pure, 3.18 g, 9.23 mmol) in CH_2Cl_2 (25 mL) was prepared and slowly added to a stirred suspension of alkene **49** (1.85 g, 9.23 mmol) and Na_2CO_3 (3.18 g, 30.0 mmol) in CH_2Cl_2 (25 mL). Stirring was continued overnight and the mixture was poured into water (100 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 5% EtOAc-hexane, gave oxirane **50** (0.98 g, 64%): R_f = 0.27; FT-IR ($CHCl_3$ cast) 1256, 1101, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.50-1.73 (m,

4 H), 2.42 (q, J = 4 Hz, 1 H), 2.69 (dd, J = 4, 1 Hz, 1 H), 2.90 (m, 1 H), 3.64 (m, 2 H); mass (CI) m/z calcd for $C_{11}H_{24}O_2Si$ 216, found 217 (M + 1). The product is best visualized on TLC plates with iodine.

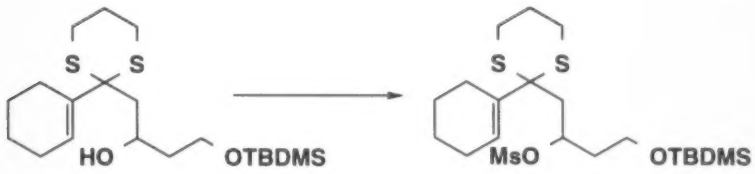
2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-hydroxybutyl]-2-[1-cyclohexen-1-yl]-1,3-dithiane (51).



n-BuLi (1.95 mL, 1.6 N in hexane, 3.1 mmol) was added to a stirred and cooled (-78 °C) solution of dithiane **48** (608 mg, 2.84 mmol) and HMPA (2.5 mL) in dry THF (10 mL). The mixture was stirred for 1.5 h while being allowed to warm to -10 °C, and then a solution of epoxide **50** (0.563 g, 2.60 mmol) in THF (2 mL plus 1 mL as a rinse) was added via cannula, using a positive pressure of Ar. The reaction mixture was stirred overnight, poured into Et_2O (30 mL), and washed with saturated aqueous NH_4Cl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexane containing 0.05% Et_3N, gave alcohol **51** (0.466 g, 43%): R_f = 0.24); FT-IR ($CHCl_3$ cast) 1098, 1064, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.03 (s, 6 H), 0.89 (s, 9

H), 1.37-1.75 (m, 8 H), 1.86-2.31 (m, 7 H), 2.65-2.95 (m, 4 H), 3.61 (m, 2 H), 3.77-3.92 (m, 1 H), 6.28 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -5.31, 18.31, 22.08, 23.32, 25.16, 25.62, 25.95, 27.10, 27.36, 28.85, 34.08, 46.35, 58.04, 63.11, 68.21, 128.61, 136.28; mass (FAB) *m/z* calcd for $C_{20}H_{37}O_2S_2Si$ (M - H) 401, found 401. The product is not stable to chromatography.

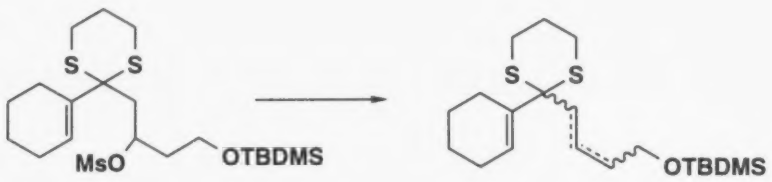
2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-hydroxybutyl]-2-[1-cyclohexen-1-yl]-1,3-dithiane methanesulfonate (52).



$MeSO_2Cl$ (0.50 mL, 0.74 g, 6.5 mmol) was added to a stirred and cooled (0 °C) solution of alcohol **51** (0.176 g, 0.421 mmol) and Et_3N (1.00 mL, 0.71 g, 7.0 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred for 2 h and then poured into CH_2Cl_2 (25 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated. The product was unstable to silica chromatography (2D TLC) in the absence of added Et_3N. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexane with 3% Et_3N, gave an oily compound tentatively assigned structure **52** (57.1 mg, 27%): R_f = 0.21;

FT-IR ($CHCl_3$ cast) 1101, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.03 (s, 6 H), 0.89 (s, 9 H), 1.51-1.76 (m, 6 H), 1.82-2.29 (m, 7 H), 2.38 (dd, *J* = 15, 6 Hz, 1 H), 2.58-2.90 (m, 4 H), 3.03 (s, 3 H), 3.60 (ap t, *J* = 6 Hz, 2 H), 4.82 (m, 1 H), 6.29 (m, 1 H).

Compound (53).



DBU (0.50 mL, 0.51 g, 3.3 mmol) was added to a stirred solution of **52** (57.1 mg, 0.115 mmol) in dry toluene (5 mL) (Ar atmosphere). The solution was heated at 100 °C and stirred for 14 h, then cooled to room temperature and diluted with Et_2O. The solution was washed with aqueous HCl (2 N, 25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated. This procedure afforded compound **53** (29.7 mg, 64%) as a homogeneous (TLC 10% EtOAc-hexane, silica) oil: R_f = 0.13, ^1H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 6 H), 0.075-0.99 (m, 9 H plus solvent), 1.05-1.45 (m, 4 H, plus solvent), 1.46-2.05 (m, 6 H), 2.05-2.30 (m, 2 H), 2.45-3.25 (m, 4 H), 3.53-3.72 (m, 2 H), 5.59-6.45 (m, 2 H), [6.53-6.62 (m, 0.4 H) and 7.51-7.69 (m, 0.6 H) total 1 H]. The ^1H NMR spectrum indicates that a mixture of double bond isomers was present, as shown above.

References and Footnotes for Part I

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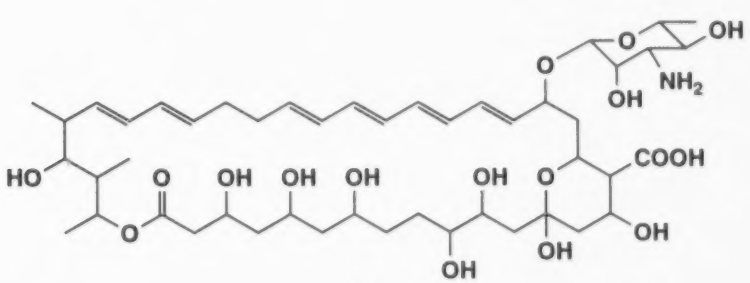
Part II

IV. Amphotericin B Mimics - Introduction

IV.1. General Introduction

The similarity between fungal and animal cells leaves few therapeutic agents that will affect one cell type and not the other. This has caused an acute shortage of effective drugs, thus amplifying the problem of dealing with fungal infections. The first reported chemotherapy against fungi (using potassium iodide as the drug[1]) was in 1903, in the case of a sporotrichosis infection, and the first antifungal antibiotic from natural sources was discovered in 1939. The compound was a secondary metabolite, called griseofulvin, from *Penicillium griseofulvum*. Nystatin (**54**), the first therapeutically useful antifungal drug active against yeasts and yeast-like fungi was reported in 1951.[2]



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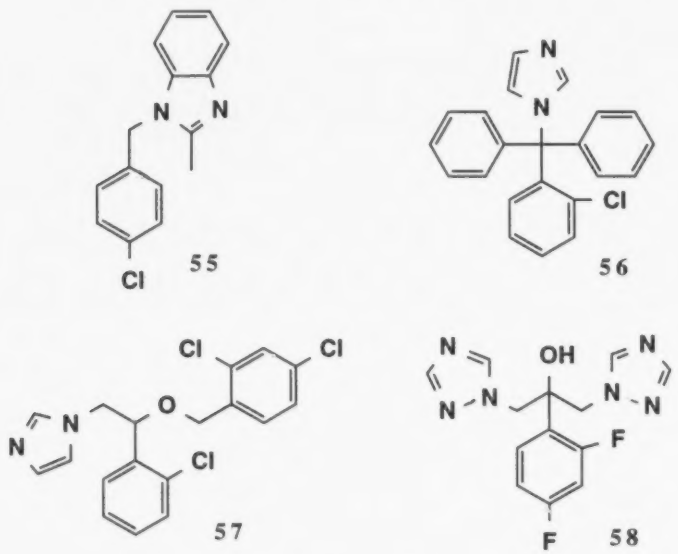
The discovery of nystatin was followed by a number of reports on similar substances produced by different members

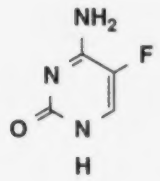
of the genus *Streptomyces*. All of the compounds are of similar structure, possessing a polyene system incorporated into a polyhydroxylated ring.

There are only a few synthetic antifungal agents, the most important being a group of compounds derived from imidazole. Important examples are chlormidazol (**55**), chlortrimazol (**56**), miconazol (**57**), and fluconazole (**58**), whose structures are shown below (Scheme 33).



Scheme 33

There is only one other synthetic antifungal drug currently in common use – a pyrimidine-based compound called flucytosine (**59**).

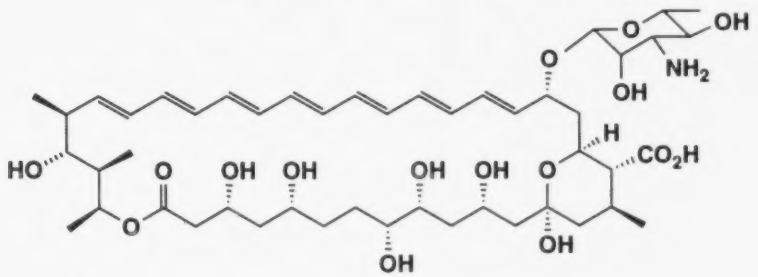


59

Flucytosine was initially designed to act as a cytostatic agent but was found to be inactive.[3] At a later date it was tested for other types of biological activity and found to be active against yeasts *in vitro*. It was also active *in vivo* in mice against candidosis, and is now usually used in conjunction with other drugs. In combination therapies it is a clinically useful antifungal agent.

IV.2. Amphotericin B and Other Polyene Antibiotics

Amphotericin B (AmB, **60**)[a] is a member of a group of about 200 antifungal agents of grossly similar structure. Of this group, the full structure and absolute configuration was established first for AmB, by X-ray crystallography.[4]



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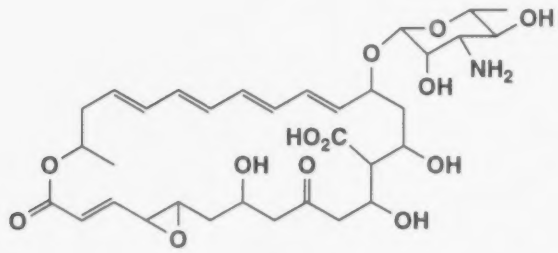
[a] AmB was isolated from *Streptomyces nodosus*, which is found in the soil of the Orinoco river valley in Venezuela. AmB is sold under the tradename Fungizone.

AmB (**60**), nystatin (**54**), and natamycin (**61**) are the only polyene macrolides that are used clinically. AmB must



61

be administered in the hospital because the therapeutic dose is very close to the toxic dose.

All members of the group are macrocyclic lactones with ring sizes ranging from about 30 to 40 atoms. The ring contains a system of conjugated double bonds, usually three to seven. The remaining portion of the macrocycle is usually highly oxygenated, normally by six to fourteen hydroxyl groups. These hydroxyls are often arranged in a 1,3-substitution pattern. Usually, there is also present at least one polar functional unit, such as a carboxylic acid, or an amino sugar, and many of the compounds possess both of these polar functionalities.

IV.3. Mode of Action of Polyene Antibiotics

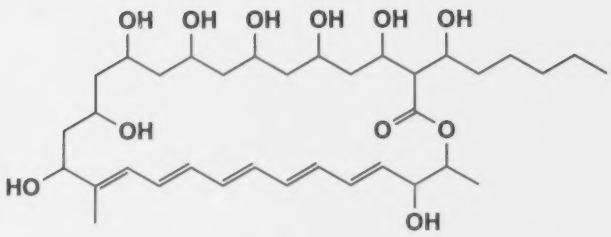
A great deal of effort has been expended to elucidate the mode of action of the polyene antibiotics, especially AmB, and there are a number of reviews on this

subject.[1,5,6,7,8,9,10] From early studies it was known that the site of action was the fungal cell membrane, and that the compounds increased the permeability of the membrane. Increased permeability disturbs the normal function of the cell and leads to cell death. A significant amount of oxidative damage is observed in cells that have been killed by AmB.[11,12] The mode of action of AmB that is generally accepted was first proposed in 1974[13,14] and has since undergone some refinements. The basic features of the mechanism are as follows:

The polyene antibiotics form complexes with steroids found in the membrane; the drug-steroid complex disrupts the membrane, causing leakage of ions and other components of the intracellular fluids, and the net effect leads to cell death. The structure of the antibiotic-steroid complex, and how it causes membrane disruption, is a function of the particular antibiotic. For the most part, the membrane disruption mechanism is postulated to be of two types that involve formation of planar arrays, or of channels, as described below.

IV.3.a. Planar Arrays of Polyene Antibiotics

An example of an antifungal agent that is thought to form planar arrays is filipin (**62**).



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The fundamental unit of the aggregate is made of two filipin molecules oriented with the hydroxyl portions (hydrophilic) towards each other and the polyene portions

Figure 1 - Filipin/Cholesterol Complex

away from each other. Several such pairs stack like slices in a loaf of cut bread, and a number of these "loaves" are arranged in a layer, with sterols binding the hydrophobic

exterior of the layer (Figure 1).

The mechanism by which this type of complex forms is not known, but it is believed that the sterols bind to the filipin first and then two sterol-filipin complexes bind by hydrogen bonds. The complex continues to grow as more pairs join up, and the driving force for formation of the aggregate is thought to be the reduction of unfavorable hydrophobic-hydrophilic interactions in the interior of the lipid bilayer.

Evidence for such structures has been found by freeze-etch electron microscopy[13] which showed areas of convex deformation of the membrane surface. It is thought that these bubbles on the surface indicate the presence of the filipin aggregates. Some of the deformations were up to 50 Å above the membrane surface. The deformations cause stress on the membrane at the edge of the bubble, and it is here that membrane rupture occurs.

IV.3.b. Channel-Forming Polyene Antibiotics

It is believed that AmB and nystatin form channels in membranes. Evidence for this phenomenon comes from studies on membranes that show quantized or gap type transmission of ions.[15] The proposed structure for the channel consists of eight polyene antibiotics alternating with eight sterols, associated in such a way that a channel with C_8 rotational symmetry is created.[16] The hydrophobic polyene portion orients towards the outside, i.e., towards the lipid

surrounding the channel, and the hydrophilic hydroxyl portion positions itself towards the center of the resulting pipe. The polyene-sterol aggregate is only long enough to span half of the lipid bilayer, and hence forms just a half-channel. When two half channels align a full channel is formed, as seen in Figure 2.

Figure 2. AmB/Cholesterol Complex Half-Full Channel Model

Hydroxyl groups at the termini of the tubular aggregates may well play a role in stabilizing the full channel structure by hydrogen bonding with corresponding groups on

another tubular subunit. The reason for the quantized transmission of ions is now understandable – only when the *full* channel is open can ions cross the membrane and escape from the cell. Thus transport of the ions is not continuous, as the full channels only form for short periods. Computer calculations on a variety of aggregation states indicated that the full channel structure (composed of two half channels) that would span the whole bilayer is more stable than the half channel.[17] Calculations also indicate that the pore size is *ca.* 4 to 8 Å.[16,17]

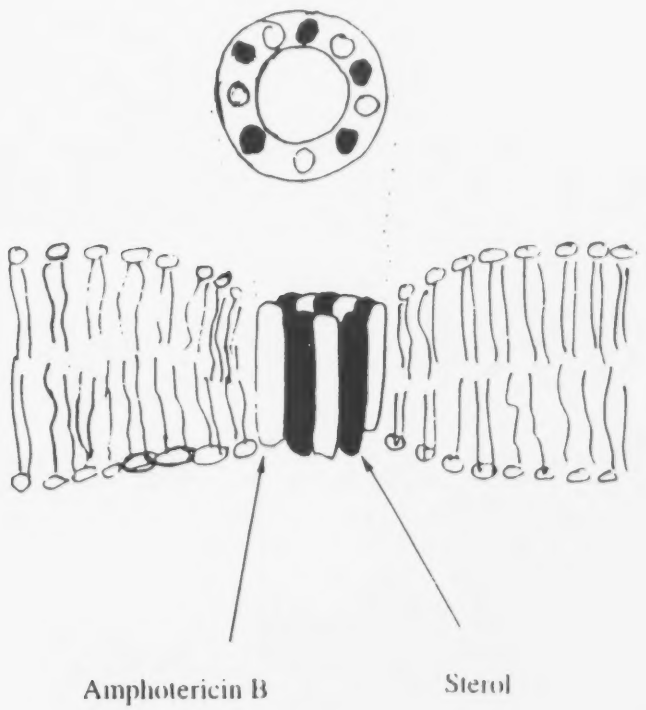


Figure 3. AmB/Steroid Complex Bolard Model

Recently, Bolard and co-workers[18] noted that the aggregation state of AmB determines which sterol it most effectively binds. The lower the aggregation state the more selective AmB is for ergosterol. Bolard and co-workers also proposed that AmB only forms the half channel, described above, and that the half channel spans the lipid bilayer and leads to ionic leakage, as shown in Figure 3. The channel model, particularly the Bolard version, is strongly supported by Hartsel and co-workers in a recent review[7] and in a recent paper.[19]

IV.4. Amphotericin B

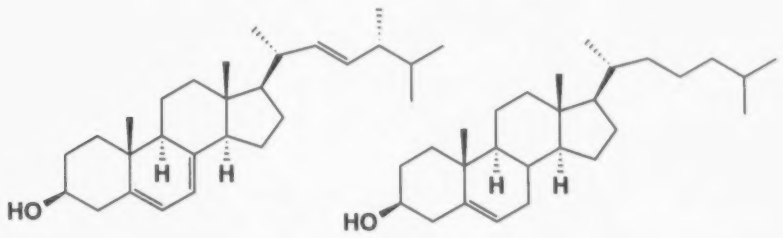
AmB is probably the most widely used antifungal agent for systemic fungal infections, but it is usually used only if the fungal infection is life threatening. As previously mentioned, AmB is very toxic, but is of relatively low toxicity when compared with other polyene antibiotics. A Japanese study[20] showed that AmB has one of the lowest minimum inhibitory concentrations (MIC) *in vitro* of the drugs used for systemic fungal infections. There has been a great deal of research carried out on AmB and some of the most relevant results to the work reported in this thesis are discussed in the following section.

IV.5. Mode of Action of Amphotericin B

The model described in section IV.3.b. above is largely accepted, and most of the information learned since the model

was proposed supports the channel hypothesis.

It was established, through the use of differential UV spectra in several solvent systems, that AmB forms complexes with sterols,[21] and it was also found that AmB exhibits a preference for complexation with ergosterol (**63**) over cholesterol (**64**). It has been shown that AmB binds



63 **64**

ergosterol about one order of magnitude better than it does cholesterol.[22] There are conflicting reports on the stoicheometry of the sterol-AmB complexes, which have been studied in solution; some authors report a 1:1 complex[23,24,25,26] while others a 2 (sterol):1 aggregate.[27] Since the situation in solution is very different from what would be found in a membrane, the relevance of these observations to the *in vivo* mode of action is not yet clear, and the main conclusion is simply that AmB binds sterols and that the binding constant for ergosterol is an order of magnitude greater than that for cholesterol.

It is thought that the aggregate is stabilized by hydrogen bonding, van der Waals interactions, a reduction in

hydrophobic-hydrophilic interactions, and stabilization of charges on the carboxylic acid functional group and the amino group on the sugar. In other words, it is likely that many different interactions cause the observed behavior, and a clear picture has not yet emerged.

The most important effect that AmB has on a membrane is that it causes increased permeability. It is known that the loss of ions from within the cell shows quantized behavior, indicating channel formation and/or an effect on existing membrane channels. Based on circular dichroism studies, it is believed that there are two types of pores formed by AmB.[28] Khutorsky suggests, based on theoretical computer calculations, that the difference is an oscillation between two low energy states caused by rotation of the AmB molecules about their long axes.[16] In one state the channel is smaller than when the AmB is in its other possible orientation.

Further studies indicate that there are two pore sizes, and it is believed that the smaller one allows leakage of urea and salts, while the larger allows leakage of molecules as big as glucose.[28] Circular dichroism studies indicate that AmB can have many arrangements in the aggregate; however, only two will induce leakage of cellular components.[29]

Depending on how the experiments have been done, there are differing opinions on how AmB and nystatin* cause leakage of ions from cells. One study indicates that the use of

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*Nystatin is believed to operate via a similar mechanism to Amphotericin B.

large unilamellar vesicles (LUV) provides a better model than the use of small unilamellar vesicles (SMV).[30]

In another study on small vesicles made with egg phosphatidyl choline, H^+/HO^- permeability was measured by potential-dependent paramagnetic probes.[31] Addition of AmB caused a moderate permeability increase. However, when both AmB and cholesterol were added to the membrane, an increase in permeability of over two orders of magnitude was observed. Curiously, when ergosterol and AmB were added to the membrane, the latter was less permeable than when only AmB was added. It was also found that the nature of the sterols (ergosterol or cholesterol) had little or no influence on the transport of K^+ ions.

It has been suggested that AmB operates by a more complicated mechanism than simple channel formation.[32] It has been found that addition of monoclonal antibodies (IgM type) to an artificial membrane containing AmB, greatly increased the lifetime of the open channel (measured by the ionic conductivity of the lipid bilayer). Consequently, it was suggested that the antibodies were stabilizing the open form of the channel. In another study,[33] when human erythrocytes were treated with AmB (at a concentration of 5 μmol/L), total inhibition of the Na^+/K^+ pump was observed, due to membrane disruption. This effect was produced by AmB concentrations that were significantly lower than those needed to disrupt artificial membranes.

Some researchers[34] question the channel hypothesis for

cation transport. It was demonstrated that nystatin (which is believed to behave similarly to AmB) associates with Na^+ ions in methanol. This conclusion is based on NMR measurements of T_1 of free and bound Na^+ ions and the ^1H NMR of the aminosugar portion of the polyene antibiotic. It was suggested that the hydrophobic environment of the bilayer would enable a shuttle mechanism for the ions to operate. However, this proposal does not account for the increased permeability for *anions* and other cellular components.

Another study[35] found that nystatin was more effective at causing K^+ ion leakage than AmB, but that AmB was lethal at lower concentrations. This suggests that the channels or pores formed by these drugs are not necessarily involved in the cytotoxic action of the drugs.

The presence of significant amounts of oxidative damage is interesting and may indicate that another mode of action is in operation. It is known that both addition of catalase or superoxide dismutase,[11] and treatment of fungal cells with AmB in a hypoxic environment[36] leads to lower death rates among the cells compared with ordinary treatment with AmB. It is also known that AmB interacts with the Na^+/K^+ pump of human erythrocytes.[33] These facts may indicate that the mode of action of AmB is much more complex than simple channel formation and subsequent ion leakage. Burnette and Hsu have found that at very low concentrations of AmB the channel opening probability of K^+ channels in the membrane of the cell is significantly increased.[37] Burnette and Hsu also

state that AmB influences the K^+-channel proteins of the cell either by direct interaction or by disruption of the surrounding bilayer, resulting in conformational changes in the protein.[37]

In conclusion, there are several variations on the channel hypothesis. It is likely that channel formation is not the only mechanism of action. The increased permeability caused by AmB leads to loss of ions and cellular components. There may also be other, poorly understood, effects which are concentration- and time-dependent[10] and are related to the oxidation of AmB or its ability to produce oxidative damage to cells.

Surprisingly, no direct statement appears in the literature, as far as we can tell, about the possibility that AmB binds (preferentially) to a fungal cell receptor.[38]

IV.6. Importance of the Functional Groups of Amphotericin B

Little is known about which functional groups cause the biological activity of AmB. A QSAR study[39] on AmB, and sixteen derivatives (chemical modifications were made at the amino and carboxyl groups) showed that the charged amino group and the sugar are important for biological activity and that the carboxyl groups plays a role in the selectivity of the drug for ergosterol over cholesterol. This type of analysis only allows one to draw conclusions on the compounds used in the study, and provides little information for other

compounds of similar structure.

IV.7. Therapeutic Use and Toxicity of Amphotericin B

Several studies[40,41,42] show that the structural requirements of the sterol for binding to AmB are a 3β-hydroxyl group, a planar ring system, and a hydrophobic chain at C-17 of the sterol. However, the most important property of AmB is that it binds ergosterol an order of magnitude more strongly than cholesterol.[22] This preference for ergosterol is why AmB can be used to cure fungal infections. Human cell walls contain mainly cholesterol, while fungal cell walls contain ergosterol. This difference explains the selectivity for fungal cells over human cells and also the reason for a lack of antibacterial activity – bacteria do not possess ergosterol in their cell walls. One needs to remember that AmB and other polyene macrolides do bind cholesterol and still will effect animal cells, and this is the reason for the observed toxicity of these substances.

Many ways have been found to reduce the toxicity of AmB, such as the administration of sucrose monolaurate, which causes a reduction in the affinity of AmB for cholesterol but not for ergosterol.[43] The formulation of the drug is also important. Tests on membranes showed that when AmB was administered in vesicles the permeability of the lipid bilayers increased. The conclusion drawn was that the vesicles had fused with the bilayer and delivered the AmB.[44] Another study showed liposomal AmB caused less K^+ leakage

from human erythrocytes than did free AmB, and that the drug was more toxic when administered in liposomal form against *Candida albicans* than in the free form.[45] Tests on mice have shown that when the drug was encapsulated using vesicles made of egg phosphatidyl choline, cholesterol, and tocopherol succinate (ratio 9:2:1), Candida infections could be treated using doses of AmB that would have been lethal if the drug was administered in its free state.[46] Encapsulation of AmB in liposomes has been put into commercial use, and liposomal AmB is now marketed as AmBisome by Vestar.[47]

IV.8. Other Biological Properties of Amphotericin B

AmB has been shown to improve the immunological response of microphages against fungi,[48] and resistance to fungal and *Staphylococcus aureus* infections, when the drug was administered before infection occurred.[49] Administration of AmB to rats before Asperigillosis infection greatly increased their survival compared with untreated rats.[50]

AmB has been shown *in vitro* to circumvent and reverse the resistance of tumor cells to administered drugs. This property of AmB has been attributed to its ability to change the permeability of the cell membrane.[51] A review has been published on the ability of AmB to enhance the cytotoxicity of anticancer drugs.[52] Amphotericin B has also been shown to have an effect on patients infected with the HIV virus.[53]

IV.9. Synthetic Work on Amphotericin B and Other Channel-Forming Compounds

Amphotericin B (**60**) has been synthesized by Nicolaou,[54] but the properties of derivatives were not studied. However, there are other studies[55] of compounds that form channels in membranes. An example is research by Fyles and co-workers,[55a] who prepared a series of compounds related to **65**, using different crown ethers, side arms, and head groups (Figure 4).

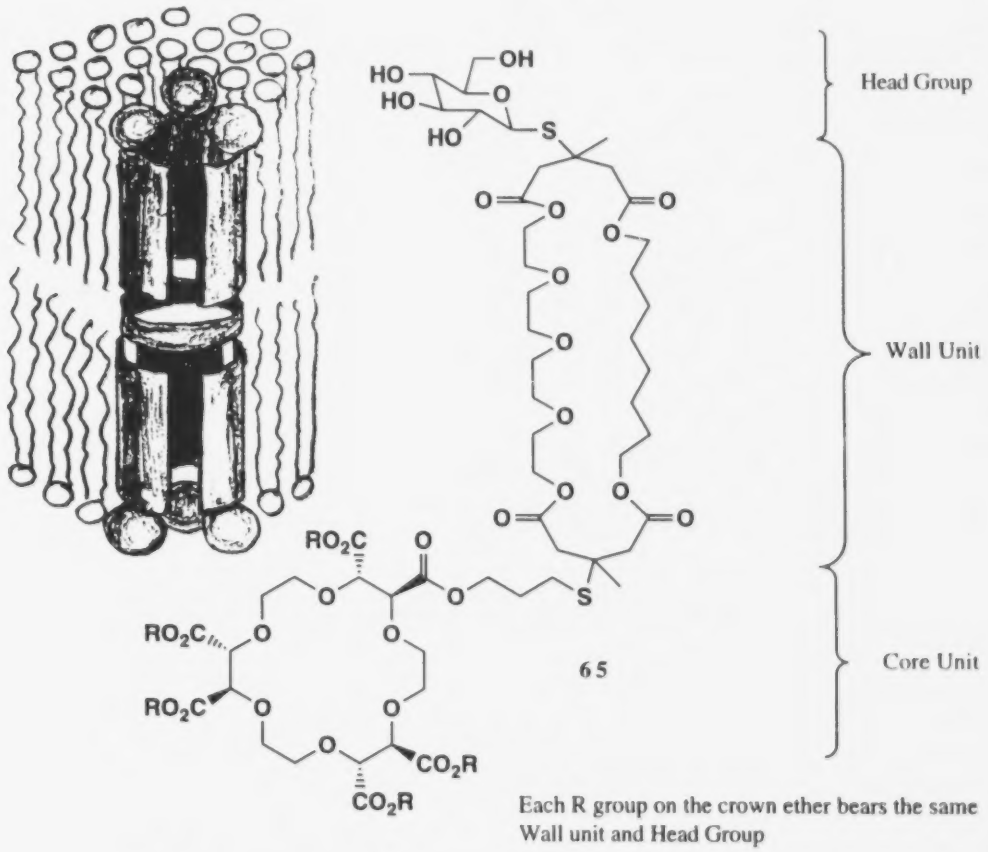


Figure 4 - Fyles's Synthetic Ion Channel(s)

They prepared a series of five core units that allowed different numbers of wall units to be attached. A second series of five different wall units and three different head groups were tried for each of the core units, leading to a total of twenty-two different compounds. The core unit of the structure helps to orient the wall units and to place them in a suitable position to form a channel-like structure. Four of the compounds showed shuttle type behavior while six of them behaved as though a channel through the vesicle had been created. Other workers have used similar strategies and, for example, Lehn's group described bouquet compounds, which also use a crown ether core unit.[55c]

Cyclodextrins have also been used as the core support, with the wall units composed of peptides.[55d] Nolte and co-workers have used a polymeric isocyanide helix to act as a backbone to locate and help orient crown ethers to form channels.[55e]

Another strategy comes from the work of Ghadiri,[56] in which a series of alternating *R* and *S* amino acids were used to prepare a cyclic peptide with groups that could hydrogen bond on the edges of the resulting cylinder (Figure 5). Several of these rings stacked in the lipid bilayer and formed a channel. The ionic conductance was quantized and this behavior was taken as evidence for the formation of channels.

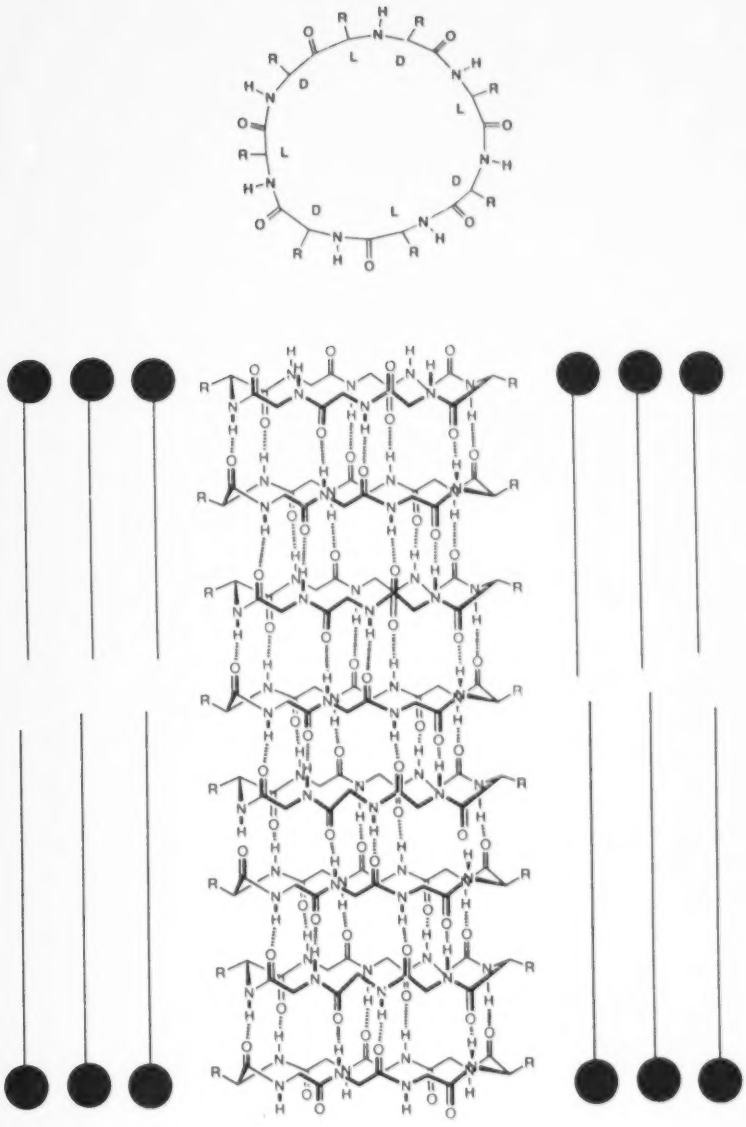
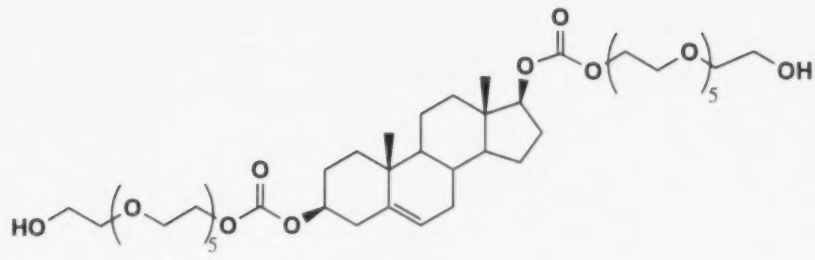


Figure 5 - Gadiri's Synthetic Ion Channel

Regen and co-workers have recently reported compound **66**, which causes Na^+ ion leakage from artificial membranes and which operates via a channel-like mechanism, as indicated by ^{23}Na NMR spectroscopy.[57]



66

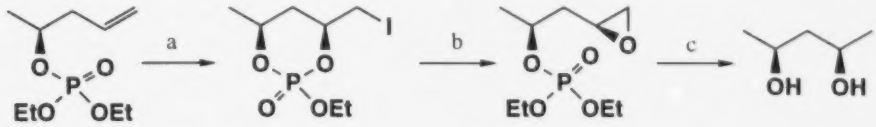
The aim of the present project was to develop a general methodology for the preparation of relatively simple compounds that might duplicate the mode of action of AmB. Some of the compounds would posses a polyhydroxy region in the macrocycle, and so a brief review of methods for the preparation of 1,3-polyhydroxy compounds is presented in the next section.

IV.10. Synthesis of 1,3-Polyhydroxy Compounds

There has been a great deal of progress in the development of stereocontrolled syntheses of 1,3-polyhydroxy systems. One of the major obstacles is that this relatively simple system offers few spectroscopic clues to allow easy proof of structure. In general, the practice has been to compare synthetic (or natural) polyols with reference compounds of known structure, and a good example of this technique can be seen in work done by Oishi.[58] The synthesis of 1,3-polyols was reviewed by Oishi and Nakatata 1990;[59] the present review will concentrate on methods that afford extended 1,3-polyhydroxy systems.

IV.10.a. Methods to Control Relative Stereochemistry of the Hydroxyl Groups

Techniques have been developed that will allow control of the relative configuration of the hydroxyl groups in the 1,3-polyhydroxy system. Cyclic intermediates have been used, involving an existing hydroxyl group, to introduce a new one that is *syn* to the first. Bartlett demonstrated that phosphate esters are suitable for this technique (Scheme 34).[60]

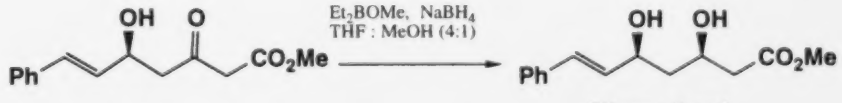


a) I_2, MeCN (87%) b) EtO^-, THF (75%) c) $LiAlH_4$ (90%)

Scheme 34

A similar strategy that uses cyclic carbonates has been developed by two different groups,[61,62] and an example of this method is discussed in the next section.

Hydride reducing agents have also been used in conjunction with complexing agents to generate *syn* 1,3-hydroxyl groups (Scheme 35).[63]

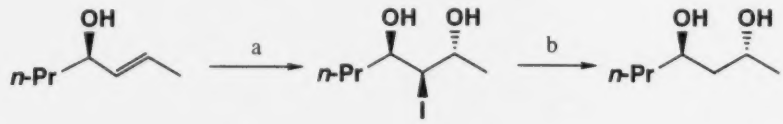


95 *syn* : 5 *anti*

Scheme 35

$Ti(Oi\text{-}Pr)_4$ and $NaBH_4$ in THF[64] are reported to give similar results, but the *syn/anti* ratio was only 87:13 compared to 95:5 in the example of Scheme 35. DIBAL has been reported to give modest asymmetric induction.[65]

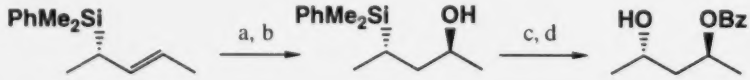
Anti 1,3-hydroxyl systems are usually prepared by two methods. Two examples of the first approach rely on stereoselective addition of electrophiles to double bonds, and the observed stereochemistry has been rationalized by Houk.[66] For example, iodohydrins have been used by Chamberlin[67] to form *anti* 1,3-diols, as shown in Scheme 36.



a) I_2, H_2O (93%, 99% diastereoselective) b) Bu_3SnH (90%)

Scheme 36

Flemming[68] has demonstrated how α-silyl olefins can be used to prepare *anti* 1,3-hydroxy compounds (Scheme 37).

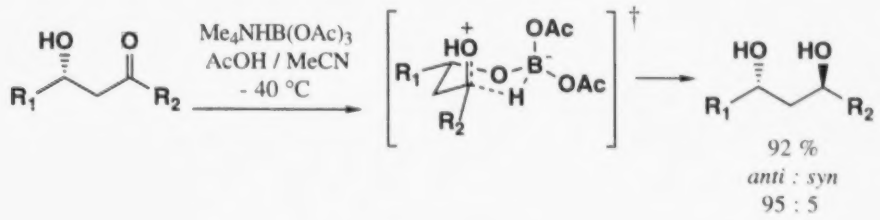


a) 9-BBN b) NaOH, H_2O_2 (96%) c) $(PhCO)_2O$, DMAP, Et_3N
d) KBr, AcOOH (71%)

Scheme 37

The most common method for preparation of *anti* 1,3-hydroxy systems is reduction of a carbonyl compound with a

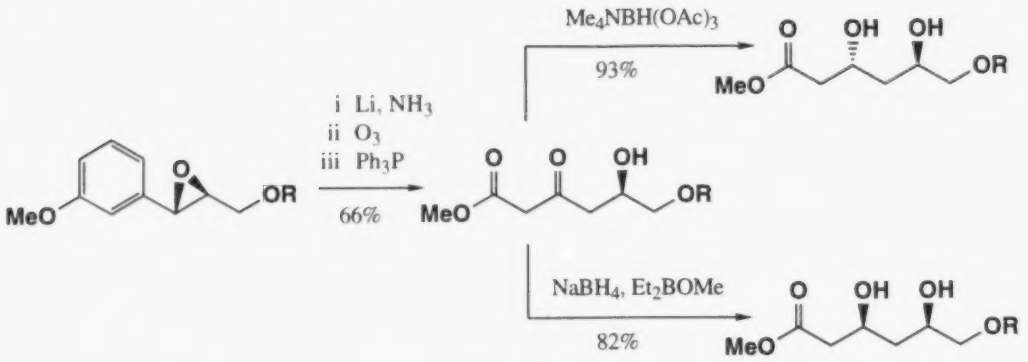
reducing agent which delivers the hydride intramolecularly. To use this method, the compound must already possess a β-hydroxyl group to complex the reducing agent. The reagent that is usually used is $Me_4NHB(OAc)_3$[69] (Scheme 38).



Scheme 38

The chair transition state (illustrated above) is of lower energy than the corresponding transition state with R_2 ($R_2 \neq H$) in the axial conformation because larger 1,3-diaxial interactions would otherwise be introduced between R_2 and the OAc group. The use of β-siloxy ketones and a Lewis acid[70] is a procedure that also operates by a similar mechanism.

More recently, Evans and co-workers[71] have demonstrated the utility of Birch reduction and chelation controlled reduction (intramolecular hydride delivery) used in tandem, as summarized in Scheme 39.

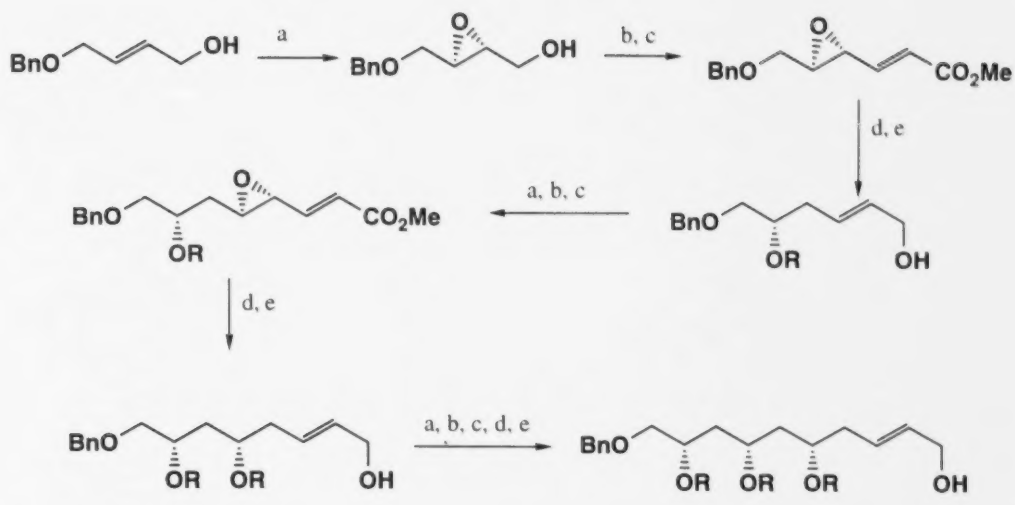


Scheme 39

The preparation of extended 1,3-polyhydroxy compounds uses many of the above methods to set the relative and absolute configuration of the various hydroxyl groups, and the strategies for creation of extended 1,3-polyhydroxy systems will now be examined.

IV.10.b. Series Approach to 1,3-Polyols

Direct use of *homoallylic* alcohols is one of the most obvious synthetic methods that has been tried. However, the degree of asymmetric induction during epoxidation or vicinal hydroxylation of the homoallylic system is usually low. To overcome this problem an iterative procedure[72] for the preparation of extended 1,3-polyhydroxy systems, based on Sharpless epoxidation of *allylic* alcohols (where good asymmetric induction is usual), has been developed (Scheme 40).



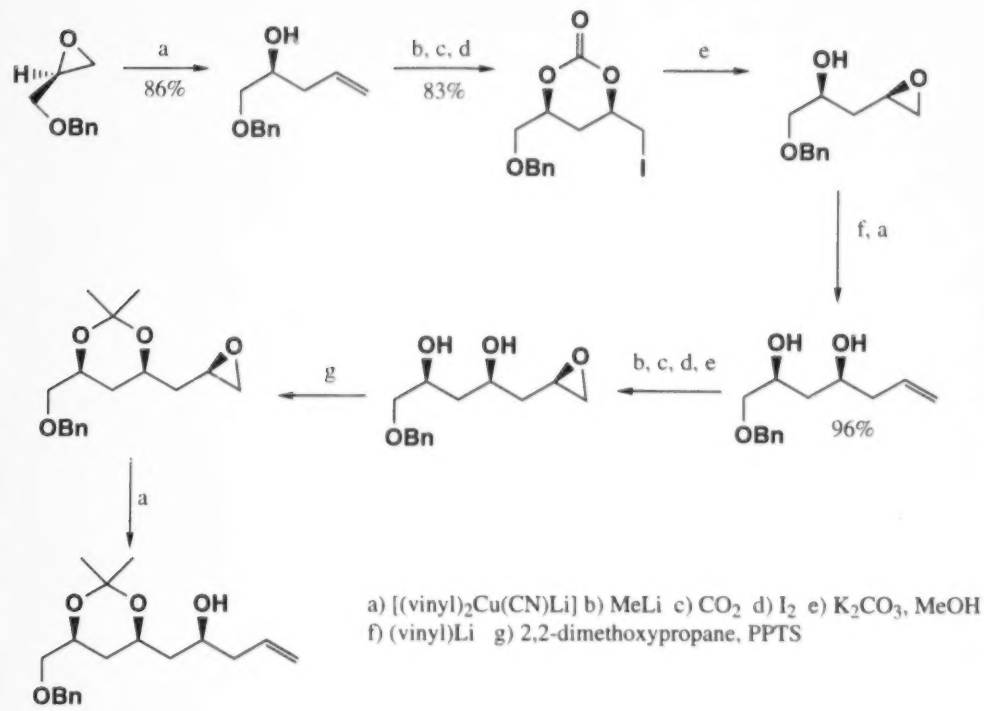
R = $SiPh_2t$-Bu

a) Sharpless epoxidation (+) diethyl tartrate, b) Swern oxidation, c) Ph_3P=CHCOOMe, d) DIBAL, e) first BOC-Cl pyridine, then Ph_2t-BuSiCl, imidazole

Scheme 40

In principle, this series of synthetic steps offers the possibility of generating an unlimited chain length of 1,3-hydroxyl groups with any stereochemistry desired – the sequence for *anti* hydroxyls is given in another paper.[73]

Lipshutz and Kozlowski[74] have developed a two-stage iterative strategy for the preparation of *syn* 1,3-diols. Their method makes use of cyclic carbonates, as previously mentioned. An example of this sequence is summarized in Scheme 41.



a) [(vinyl)$_2$Cu(CN)Li] b) MeLi c) CO_2 d) I_2 e) K_2CO_3, MeOH
f) (vinyl)Li g) 2,2-dimethoxypropane, PPTS

Scheme 41

This method is very elegant; however, it has one drawback – it allows only the synthesis of all *syn* systems.

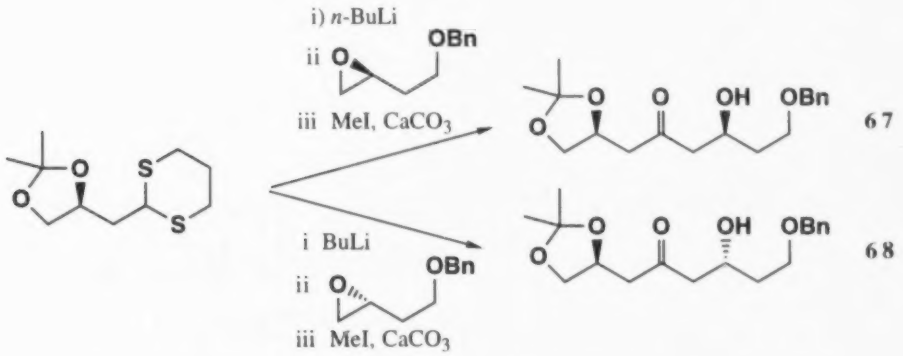
There are some disadvantages to the iterative approach to 1,3-polyhydroxy compounds. The large number of steps used to introduce each hydroxyl group makes this approach very labor intensive and the linear nature of the procedure means very large scale reactions are necessary in the beginning of the sequence.

IV.10.c. Convergent Approach to 1,3-Polyols

Use of a convergent approach to 1,3-polyols has many advantages over a linear approach. The most notable is that

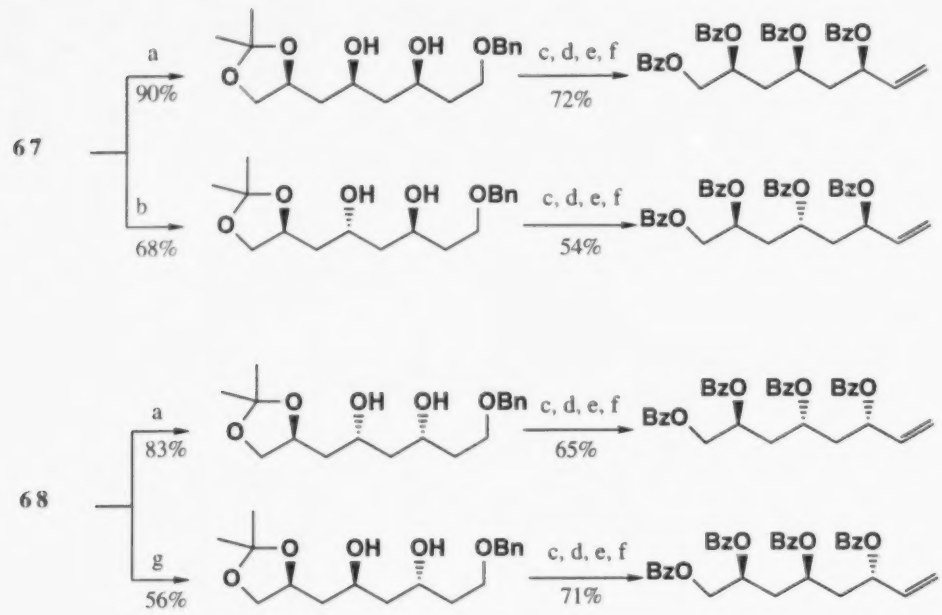
smaller subunits of the desired compound can be prepared and then assembled. This is desirable because it keeps the scale of the reactions smaller, although the number of steps is not necessarily decreased.

Mori and co-workers have demonstrated the utility and scope of this approach.[75,76] Their most recent paper[76] clearly shows the power of the approach, as they were able to prepare four diastereoisomers of an octane-1,2,4,6,8-polyhydroxy system. The first steps of the sequence are summarized in Scheme 42.



Scheme 42

By using appropriate starting materials from the chiral pool, Mori and co-workers are able to set up the desired stereochemistry in the products shown (Scheme 42). The carbonyl is then reduced using technology discussed in section IV.10.a. in order to set the configuration of the new asymmetric center as desired – either *syn* or *anti* to the existing free hydroxyl group (Scheme 43).



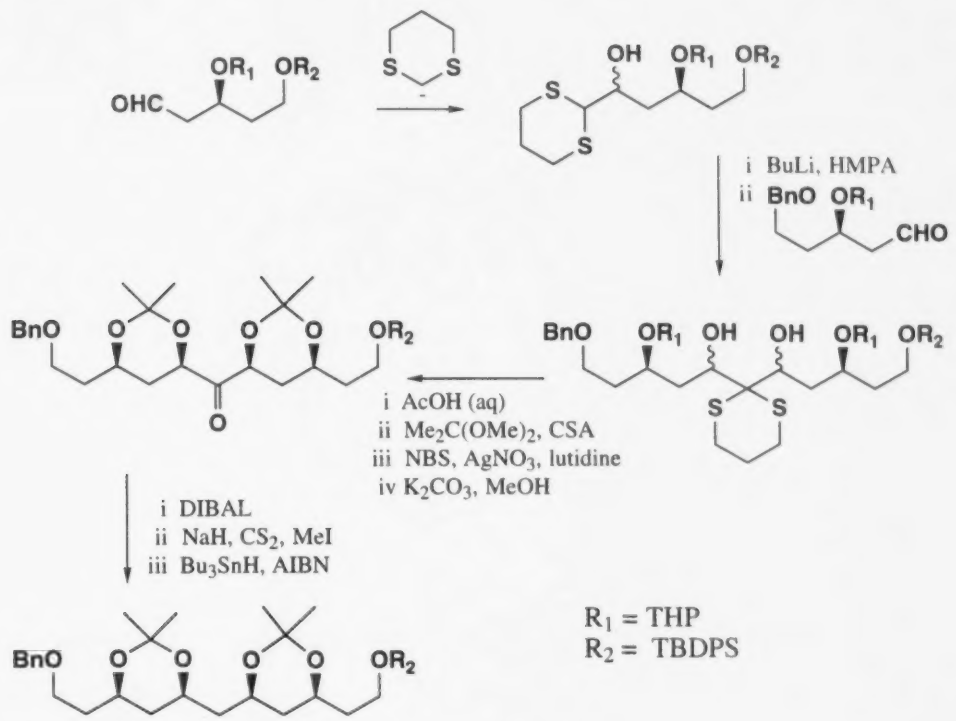
a) $NaBH_4$, Et_2BOMe b) $Me_4NBH(OAc)_3$ c) H_3O^+ d) BzCl, pyridine
e) H_2/Pd/C f) NO_2-C_6H_4-SeCN then H_2O_2 g) $LiAlH(Oi\text{-}Bu)_3$, LiI

Scheme 43

This study was done so that the compounds could be evaluated by CD and, for this reason, the hydroxyls were protected as benzoates. Note that an olefin was introduced at one terminus of the chain, in order to allow an aldehyde group to be readily generated at that position.

The ability to create hydroxy aldehydes is an important theme in the convergent approach to 1,3-polyols. A good example that illustrates the technique is found in research by Oishi and co-workers,[77] who used a dithiane to join two smaller fragments similar to those described above (*cf.* Scheme 43). Scheme 44 shows only the key step where the

fragments are linked and the stereochemistry adjacent to the linking point is set.

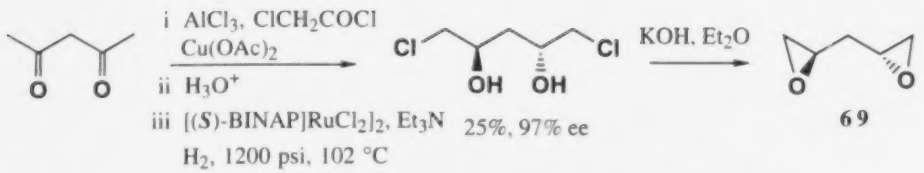


Scheme 44

There is one major drawback to this method in that the stereochemistry of the hydroxyl groups is set by a thermodynamic equilibration. The most stable isomer is the *syn* isomer in the isopropylidene system and hence only it can be obtained readily. This restriction limits the number of possible substrates that can be made by the method.

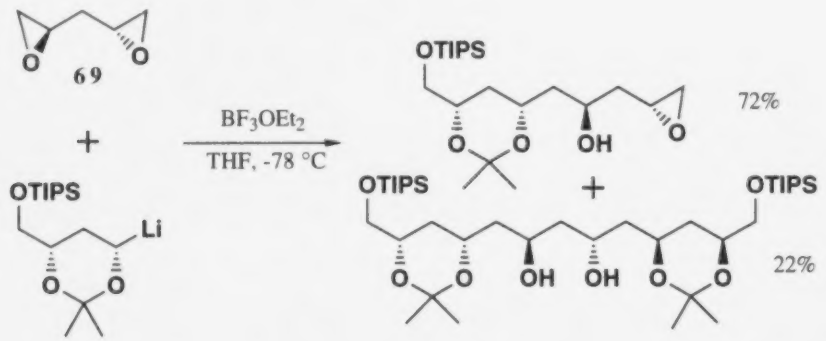
Rychnovsky and co-workers[78] have also demonstrated how a convergent approach can be used to prepare a wide variety of different optically pure 1,3-polyols. The synthesis starts

from bis epoxide **69**, which is readily prepared by the method shown in Scheme 45.



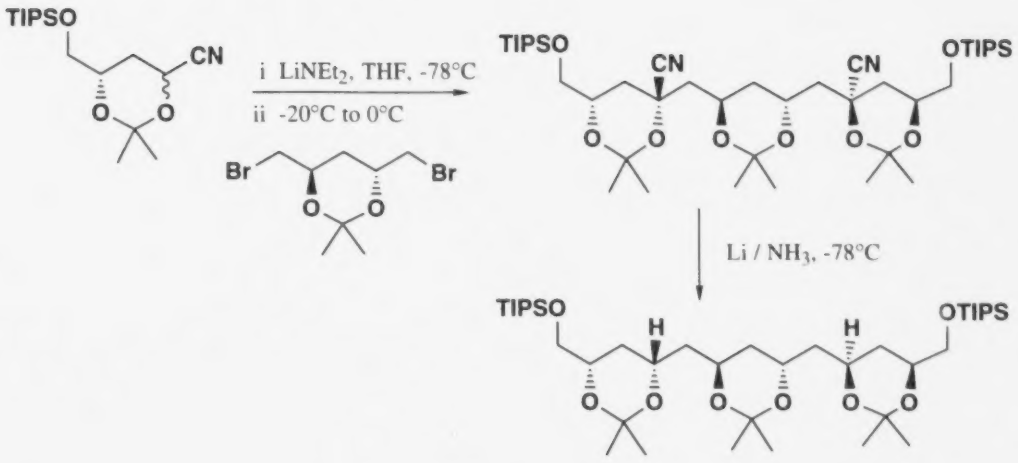
Scheme 45

The bis epoxide **69** is used to alkylate a series of nucleophiles, and the following example (Scheme 46) illustrates the method.



Scheme 46

Rychnovsky and co-workers[79] have also demonstrated how 1,3-polyhydroxy compounds can be prepared convergently, using 1,3-diol acetonides, as summarized in Scheme 47. This method



Scheme 47

allows quick preparation of extended polyhydroxy systems, although a price is paid in that not all possible relative stereochemistries are accessible.

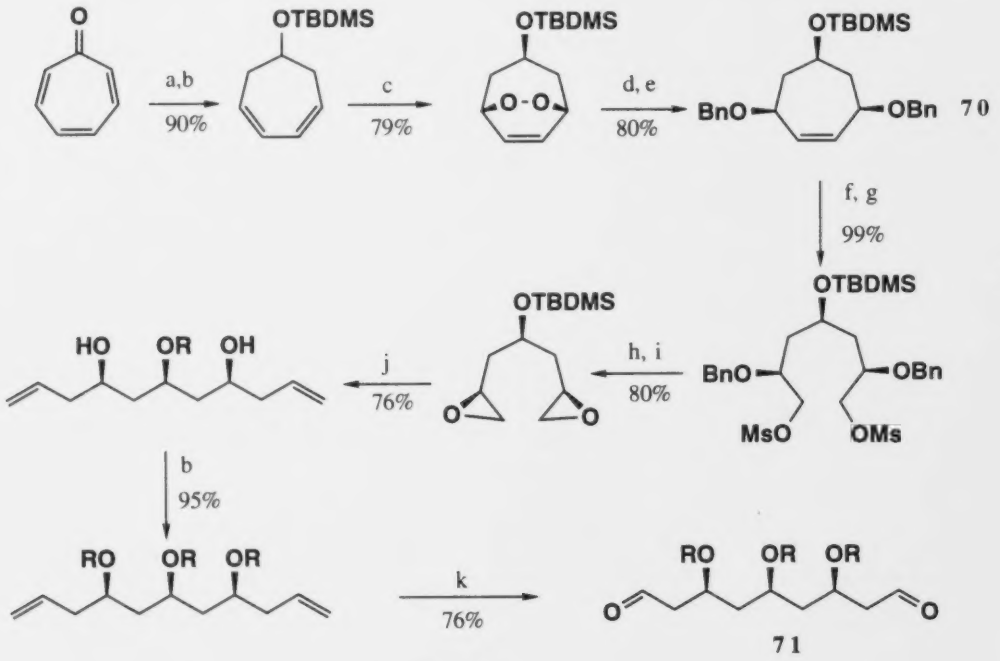
Convergent routes are quite powerful, allowing (i) a reduction in the scale of reactions at the beginning of the sequences, (ii) the use, in many cases, of simpler substrates, and (iii) the number of synthetic steps to sometimes be reduced.

IV.10.d. Bidirectional Approach to 1,3-Polyols

Schreiber has developed a synthetic approach to symmetric molecules which he has termed "two directional synthesis". This approach has many advantages in that it reduces the number of overall steps and the number of purification steps, and can improve the isomer ratio of products as compared to other methods.

Bidirectional synthesis does have one drawback, which is

that it is limited to symmetric (or closely related)[80] compounds. Schreiber and Goulet have published an example[81] of an extended 1,3-polyol system in which they extended the methodology of Floyd and co-workers.[82,83] The latter demonstrated how the triacetate-protected analog of compound **70** (Scheme 48) could be prepared. Schreiber's reaction sequence is summarized in Scheme 48.

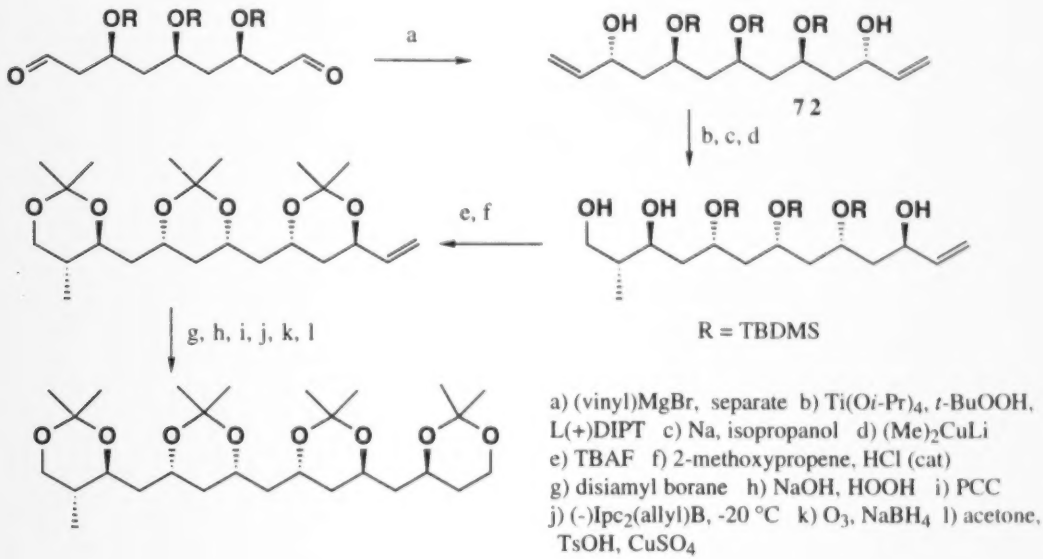


a) $NaBH_4$ b) TBDMSCl, imidazole c) O_2, CH_2Cl_2, *meso*-tetraphenylporphine, 0°C, hυ
d) Zn, HOAc e) BnBr, NaH f) O_3 then Ph_3P g) $MeSO_2Cl$, Et_3N h) $Pd(OH)_2/C$, H_2
i) K_2CO_3, MeOH j) $(vinyl)_2CuLi$ k) O_3, then Ph_3P

Scheme 48

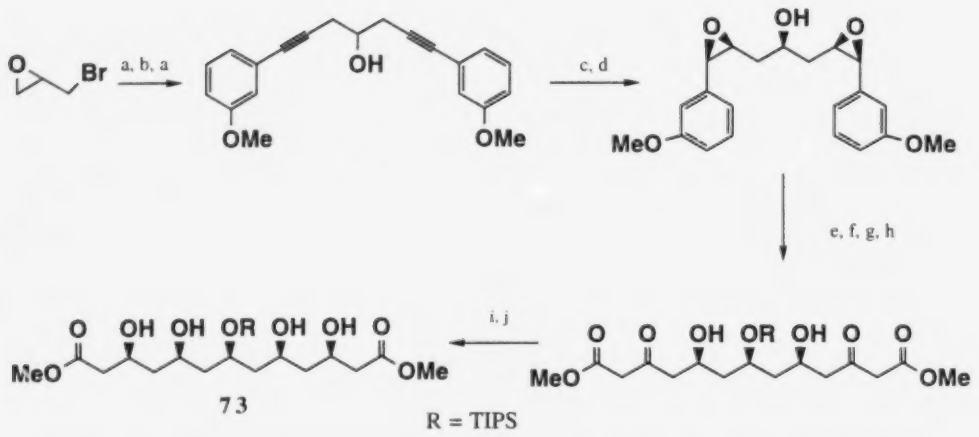
With bis aldehyde **71** in hand, it was then possible to differentiate the termini of the *meso* compound by chain

extension and further Sharpless epoxidation to afford different optically pure isomers of an extended 1,3-polyol system. This sequence is shown in Scheme 49.


OR OR OR
a
OH OR OR OR OH
72
b, c, d
e, f
OH OH OR OR OR OH
R = TBDMS
g, h, i, j, k, l
a) (vinyl)MgBr, separate b) Ti(Oi-Pr)4, t-BuOOH, L(+)DIPT c) Na, isopropanol d) (Me)2CuLi
e) TBAF f) 2-methoxypropene, HCl (cat)
g) disiamyl borane h) NaOH, HOOH i) PCC
j) (-)Ipc2(allyl)B, -20 °C k) O3, NaBH4 l) acetone, TsOH, CuSO4

Scheme 49

There is an another example by Wang and Dechênes[84] that demonstrates how bidirectional synthesis can be used to prepare all *syn* 1,3-polyols. They use Sharpless epoxidation of a homoallylic system and then Evans's method[69] of combining Birch reduction and selective delivery of hydride in a tandem fashion. The first part of the sequence is summarized in Scheme 50.



a) lithium (3-methoxyphenyl)acetylide, BF_3 b) KOH, Et_2O c) Ni_2B, H_2, EtOH d) $VO(Oi\text{-}Pr)_3$, *t*-BuOOH e) TIPSOTf, Et_3N f) Li, NH_3 g) O_3 h) PhP_3 i) Et_2BOMe, -78°C j) $NaBH_4$

Scheme 50

A 15:1 ratio of the bis epoxide shown to the other three possible products was obtained, using $VO(Oi\text{-}Pr)_3$ under Sharpless epoxidation conditions. This is a good result when compared with many other examples which can have stereoselectivities of as low as 1.5:1 for the *syn/anti* ratio. The last compound shown (**73**) was reduced, after protection, to the corresponding bis aldehyde. This was then alkylated using several optically active pinene allyl boranes in a sequence that was similar to the method Schreiber used to differentiate the ends of *meso* compound **72** of Scheme 49.

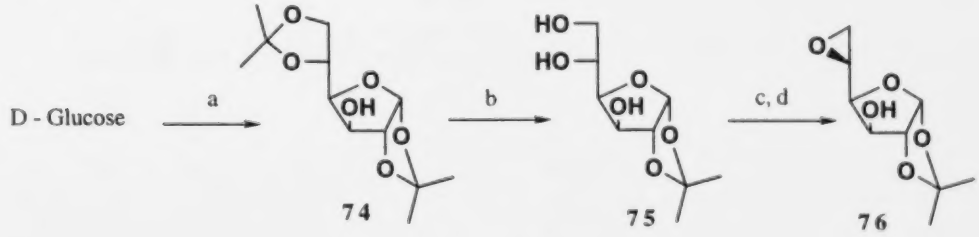
As can be seen, there is a wide variety of methods for preparing extended 1,3-polyols, and each method has its own advantages. In general, the more flexible the method with respect to *syn/anti* control, the higher the cost in terms of an increased number of steps. It now appears that the technology to prepare any desired 1,3-polyol either exists or

will very soon be developed.

IV.11. Use of Carbohydrates as the Source of the Polyhydroxy Region of Amphotericin B Mimics

We thought that a ready source of hydroxyl groups for our planned AmB mimics would be carbohydrates. Sugars seemed a reasonable source for the polyhydroxy portion of the mimic because very little structural information is available on the polyene antibiotics and the known structures showed no obvious relation between stereochemistry and/or number of hydroxyl groups and biological activity.

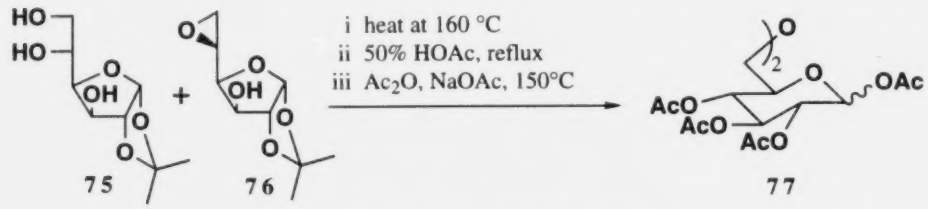
The types of reactions we wished to carry out on the carbohydrates are unusual and very little work has been reported in these areas. The first task was to join two sugars at the 6 position. There is one reference in the literature to this type of 6',6-diglyose anhydride. Whistler and Frowein[85] prepared two examples of this type of disaccharide (Schemes **51** and **52**).



a) acetone, H_2SO_4 b) 4% HNO_3 in EtOAc c) TsCl, pyridine d) MeONa, MeOH, $CHCl_3$

Scheme 51

The first step involved preparation of the 5,6-anhydro sugar **76** in the above sequence. The 1,2-isopropylidene glucopyranoside **75** and the 5,6-anhydro sugar **76** were heated in a melt, hydrolyzed, and then derivatized as the octa-acetate, to give the desired disaccharide **77**. The preparation of glucose 6',6-anhydro disaccharide octa-acetate (**77**) is shown in Scheme 52.



Scheme 52

A galactose-glucose example was done similarly. Whistler also indicated that carrying out nucleophilic substitutions at the C-6 position with other sugars was difficult.

For our own work it would also be necessary to carry out a chain extension of the disaccharide at the anomeric centers. There are only a few methods known for such chain extensions. The most common reason for forming a C-C bond at the anomeric carbon is to prepare carbon glycosides (*C*-glycosides). This subject was recently reviewed by Postema[86] and will not be covered further.

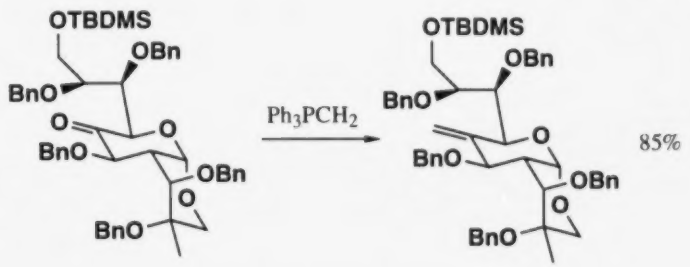
One of the first and oldest methods for chain extending a sugar is the Kiliani synthesis. The sugar is treated with

cyanide ion to give a 1:1 mixture of isomeric cyanohydrins, in which the chain has been extended by one carbon (Scheme 53).

Scheme 53

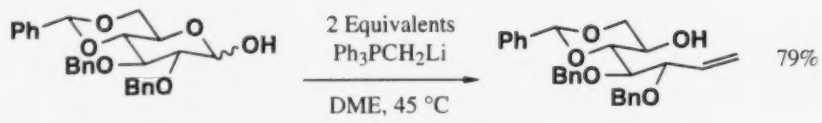
However, since only one isomer (or a preponderance of one isomer) is usually desired, this method would be of little use for the task at hand.

Wittig reactions have been carried out on sugar ketones and aldehydes. An example of such a reaction was reported by Fraser-Reid and co-workers[87] and is summarized in Scheme 54.



Scheme 54

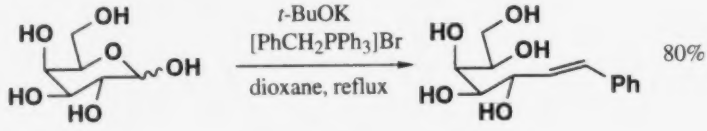
Another example[88] (Scheme 55) demonstrates how a similar reaction can be carried out at the anomeric position.



Scheme 55

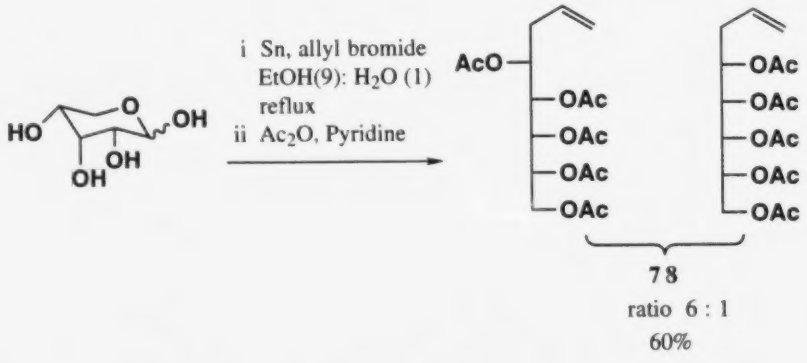
This type of step is a common one[86] and is usually a prelude to *C*-glycoside formation by treatment with I_2.

There is one very interesting set of examples[89] of a Wittig reaction on several unprotected sugars, and the case of D-galactose is summarized in Scheme 56.



Scheme 56

There are also several reports of the use of sugars as substrates for Barbier coupling.[90] A typical example involves the use of allyl bromide and tin in an aqueous solvent system (Scheme 57) to generate chain extended olefins **78**.



Scheme 57

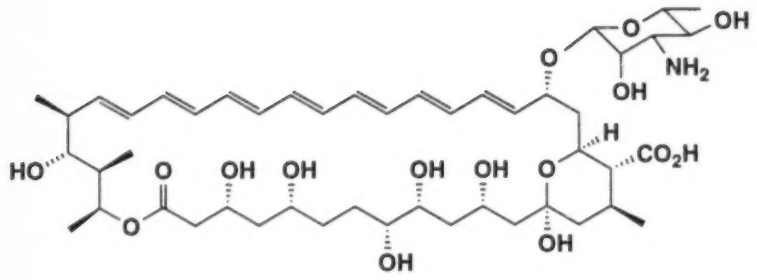
V. Amphotericin B Mimics

Results and Discussion

V.1. General Introduction

The goal of this project was to identify, through the methods of synthesis, what main structural features of AmB (**60**) are largely responsible for its antifungal action. Our approach was to attempt to prepare simpler analogs and test them for biological activity and/or for the ability to damage artificial membranes containing ergosterol (**63**), which is a component of fungal cell membranes. Ideally, a series of analogs would be prepared which contain progressively more and more of the structural features of AmB. Hopefully, this procedure would allow us to identify which features are essential for biological activity. Since AmB is a clinically important drug a better understanding of its mode of action will have medically important practical applications.

The analogs we wanted to make are based on the following considerations: an examination of the structure of AmB reveals some obvious features. These include an overall length approximately equal to half the width of a lipid



60

bilayer. AmB also possesses a rigid polyene backbone in one half of the macrocycle. The remaining portion of the lactone ring comprises a 1,3-polyhydroxy chain. The compound also has an amino sugar which probably acts as a polar head group. Since very little structure activity work has been done on AmB, we felt a rigorous imitation in our models of the steric relationships between the functional groups was not warranted at this stage.

Our plan was to develop general methodology for the construction of a series of molecules of simpler structure, but which contained some of the gross features of AmB.

We placed some restrictions on our initial targets. The first was a size constraint: The target had to be of similar size to AmB – that is of appropriate length to span half a lipid bilayer. The polyene backbone was to be retained to provide overall rigidity.

While the polyene was selected on the basis of analogy with AmB and the fact that the polyene is easily constructed, we also appreciated that the polyene system of the compound

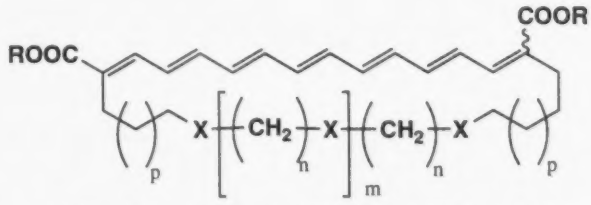
may play a role in redox chemistry as part of the mechanism of action. We intended to span the polyene chain with a series of different segments bearing different functional groups to reveal the effects of such changes on behavior. This meant that the synthetic route had to be flexible enough to accommodate different functional groups in the bridging chain as well as different chain lengths.

CPK space filling models of a number of potential analogs were made and compared to a CPK model of AmB itself. AmB, when viewed from above the macrocyclic ring, has a rectangular shape, and is planar when viewed from the side. When the models of potential targets were examined, two interesting effects were found when the chain length of the hydrophilic bridge was changed. If the chain length was too long the rectangular shape became similar to that of an upper case **D**, that is, the rectangle would bow out on the bridge side. If the chain were too short the bridge would start to twist into an **3**-like shape. One end of the bridge would be above the plane of the polyene system and the other would be below the plane of the polyene system. It was decided that a bridging chain of seventeen carbon atoms represented the best compromise between these two situations. [For other atoms in the chain, the optimum length is different.] We still intended to prepare larger and smaller rings but decided to use what we felt was the best situation (17 atoms) as the starting point. We also wanted to keep the functional groups of the analogs in the similar general regions of the

macrocycle as AmB's polyhydroxy region.

The functional groups chosen need to satisfy the following properties: they should stabilize the channel that is formed, and should allow the possibility of self assembly. The hydroxyl groups of AmB satisfy these criteria because the aggregate can be stabilized by hydrogen bonding. Hydrogen bonding could also aid self assembly, and hydroxyl groups would also help improve water solubility of the analogs.

We did not limit ourselves to the use of hydroxyl groups, however. Daroszewski,[91] had previously prepared some analogs without hydroxyl groups, and the present project is a continuation of his work. The types of compounds that were initially required have the following general structure (Scheme 58):



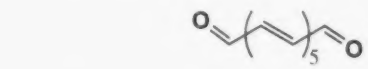
X = O, S, S=O, and CHOH m, n, p = 0, 1, 2, 3 ...

Scheme 58

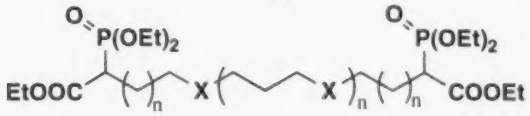
Daroszewski prepared compounds where X was O, S, or sulfoxide, with three carbons between each heteroatom. The compounds were not biologically active, but were not tested for their ability to damage artificial membranes. The remaining members of the series, the polyhydroxy compounds,

still had to be prepared, and most of our experiments were directed toward this end.

The general approach to compounds of the type shown in Scheme 58 involves preparation of polyene bis aldehyde **79**,



79



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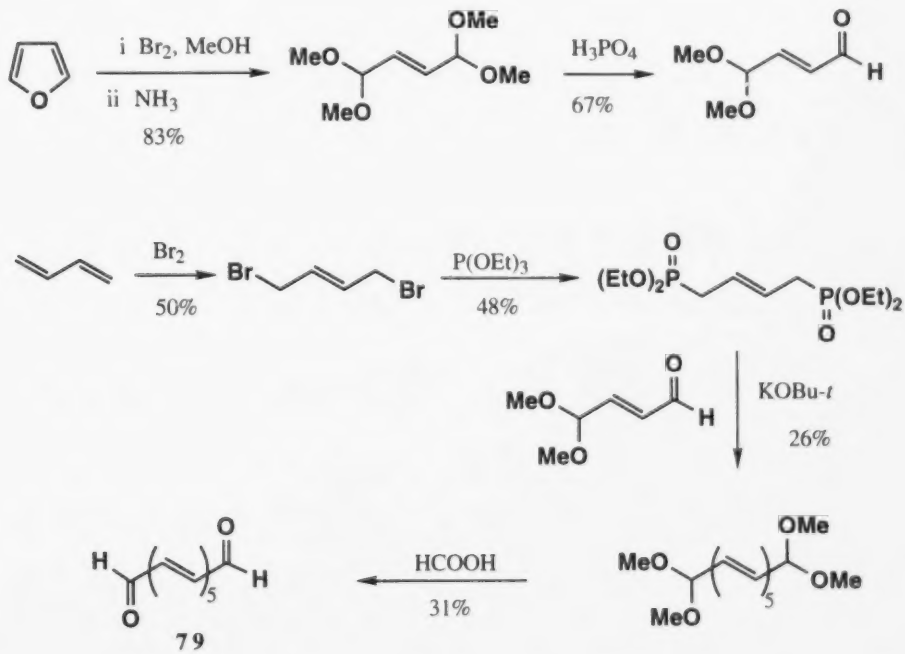
which is reacted with bis phosphonate **80**, containing variable groups X (see below).



79

Scheme 59

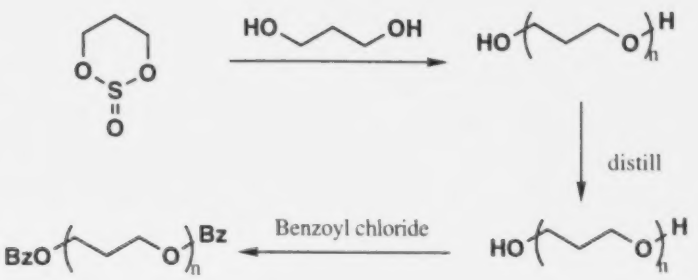
Daroszewski had demonstrated how to prepare the required polyene bis aldehyde **79**. Its synthesis is summarized in Scheme 59, and a supply of bis aldehyde **79** was available by this method.

The required bis phosphonates had to be prepared in a way that would allow for the use of various bridging chains, and a two-directional synthetic approach seemed best. The chain needed to have a functional group at each end for introduction of the phosphonate units, because the general strategy was to prepare the oxygenated portion of the bridge and then introduce the phosphonates last. Alternatively, the functionalized region of the chain could be prepared in a convergent approach leading to a compound with a common group on each end that would allow introduction of phosphonates in a two-directional sequence. Both of these approaches towards the preparation of bis phosphonates are described in this thesis.

An attempt was also made to improve Daroszewski's preparation of 1,3-polyethers.

V.2. Preparation of 1,3-Polyethers

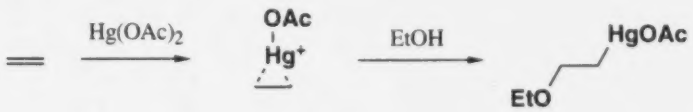
Daroszewski had used a statistically random method to prepare 1,3-polyethers.[91] The following reaction sequence (Scheme 60) was carried out to produce a mixture of many different polyethers from which the desired one was separated.



Scheme 60

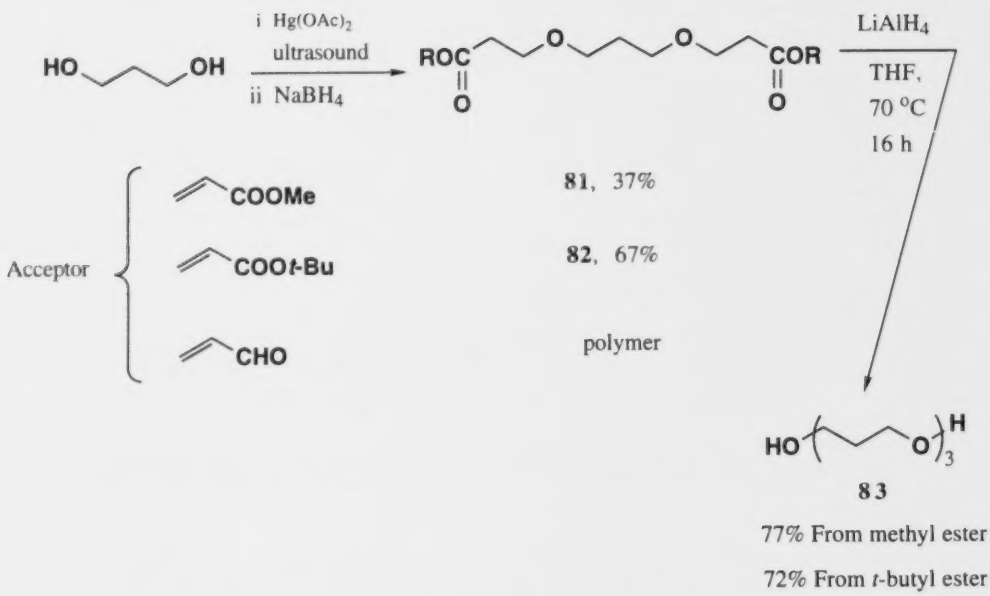
Daroszewski's separation involved rough purification by distillation to separate low molecular weight species, followed by bis benzoylation to allow purification by an arduous preparative HPLC procedure.[91] It was felt that a more controlled approach was possible so that the purification problems could be avoided.

Addition of an alcohol to mercuronium ions generated by treatment of an olefin with $Hg(OAc)_2$, as shown in Scheme 61, is a well-known process,[92] and a procedure based on this



Scheme 61

reaction was developed. The method requires three steps to generate the trimer from the monomeric diol, and then the pentamer is produced from the trimer. Preparation of the trimeric polyether **83** is summarized in Scheme 62.

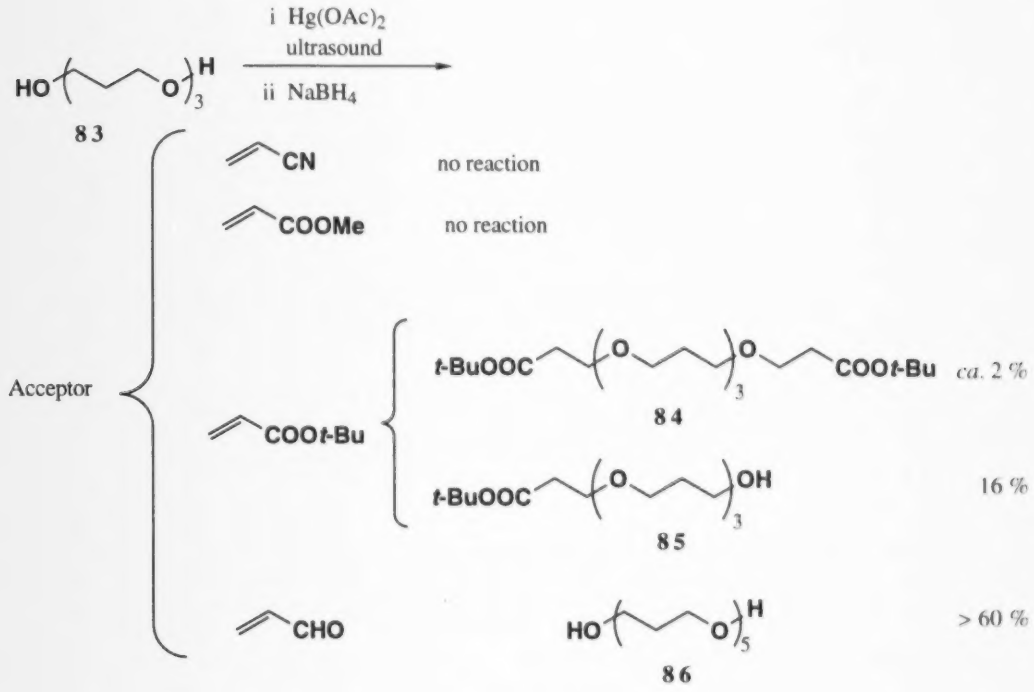


Scheme 62

The first step calls for treatment of the acceptor compound with $Hg(OAc)_2$ in the presence of 1,3-propanediol. The reaction requires sonication and affords an organomercurial which is then reduced to the bis ester **81** (or **82**) by $NaBH_4$. The bis ester is then reduced with $LiAlH_4$ to the trimeric polyether **83**.

When methyl acrylate was used as the acceptor, only a 37% yield of the bis(methyl ester) was obtained; the reason for the low yield may be ester exchange. When *t*-butyl acrylate was used as the acceptor, the yield rose to 67%, but when acrolein was used, only polymeric material was obtained. The use of ultrasound was found to be an effective way of increasing the rate of the reaction without heating. All of the acceptor compounds polymerized, as expected, when heated.

The pentameric polyether **96** was made in a similar way, as illustrated in Scheme 63.



Scheme 63

The first acceptor tried for extension of the trimeric diol was methyl acrylate, but no addition of alcohol **83** was observed. It is not clear if this was due to ester exchange or to a lack of reactivity of diol **83**. When *t*-butyl acrylate was used a small amount (*ca.* 2% yield) of the pentameric bis ester **84** was isolated as well as a slightly larger amount of the tetrameric monoester **85** (16% yield). The low yields were attributed to a lack of reactivity of the trimeric polyether **83** as compared to 1,3-propanediol. Acrylonitrile was then tried and found not to react. However, acrolein gave greater

than 60% yield (^{1}H NMR estimate on a partially purified sample) of the pentameric polyether **86**. The exact yield could not be calculated because the material was contaminated with a polymer derived from acrolein. The pentamer **86** was purified by a washing procedure through flash chromatography grade silica gel. Elution of the desired compound was accomplished by washing the silica gel, using solvents of increasing polarity while monitoring the effluent for the desired compound by TLC. The majority of the pentamer **86** was removed from the polymer when acetone was used, although the pentamer could be seen in other fractions by TLC. The material from the wash still contained some polymer, and it was found that derivatization of the diol **86** as its bis benzoyl ester allowed separation from the polymer by flash chromatography. The bis benzoate, obtained by a different route, had previously been converted into the corresponding pentameric diol by Daroszewski.[91]

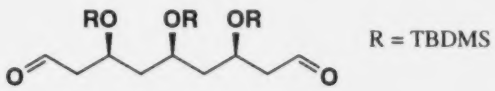
The above methodology demonstrates that the preparation of polyethers in a controlled manner is possible, and that the arduous separation problems when a statistical approach is used, can be avoided. Preparation of higher homologs was not attempted, as these were not needed for the present work.

V.3. Introduction to 1,3-Polyol Analogs

As mentioned in section V.1., an AmB mimic with a polyhydroxy system was one of our synthetic targets. Since there is no obvious relationship between the stereochemistry

of the polyhydroxy system of the polyene antibiotics and their biological activity, it appeared that we did not, at this stage, have to restrict ourselves to any particular stereochemistry of polyhydroxy compound. It was felt that retaining the 1,3-polyol system of AmB would be beneficial and, since most of the hydroxyl groups on the compound have a *syn* relationship, the preparation of an all *syn* analog appeared to be a good starting point.

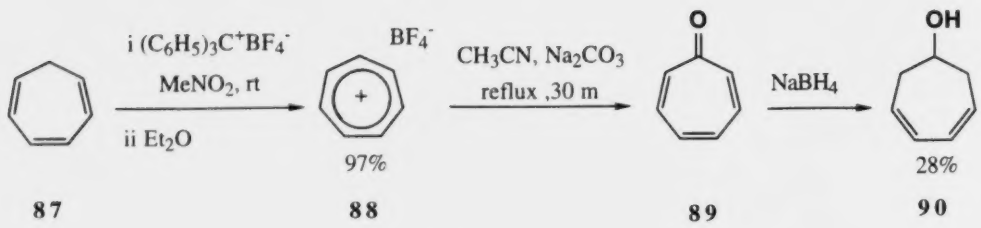
In a preliminary communication,[81] Schreiber and Goulet had demonstrated how the all *syn* 1,3-polyol bis aldehyde **71** could be made (the whole synthetic scheme is shown above in section IV.10.d.). Few experimental details were provided in



71

the communication, but the reagents were given, and the synthesis of the bis aldehyde **71** was carried out as described in the following paragraphs.

The sequence started from tropone (**89**) which was prepared from cycloheptatriene (**87**). Tropone is susceptible to decomposition via a Diels-Alder reaction, and its distillation was avoided by not isolating the compound. The reactions used to prepare alcohol **90** are shown in Scheme 64.

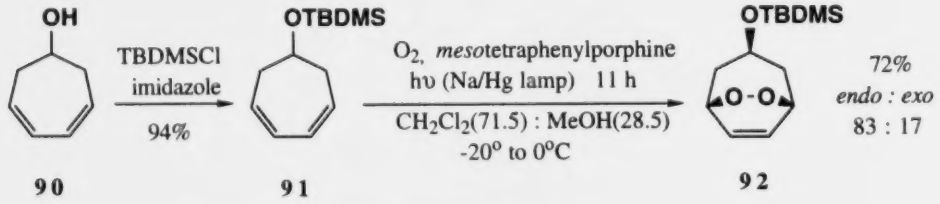


87 **88** **89** **90**

Scheme 64

Tropylium tetrafluoroborate (**88**) was made by treating cycloheptatriene with the triphenylmethyl cation. In an unusual oxidation,[93,94] Na_2CO_3 converted the tropylium salt to tropone (**89**), which was reduced without isolation to the cyclic alcohol **90**. The mechanism of the oxidation is unknown,[93,94] although a disproportionation of the cation occurs to regenerate cycloheptatriene along with tropone. Interestingly, we found that K_2CO_3 will not oxidize the cation.

Having the required alcohol **90** in hand, the preparation of bicyclic peroxide **92** was carried out as in Scheme 65.

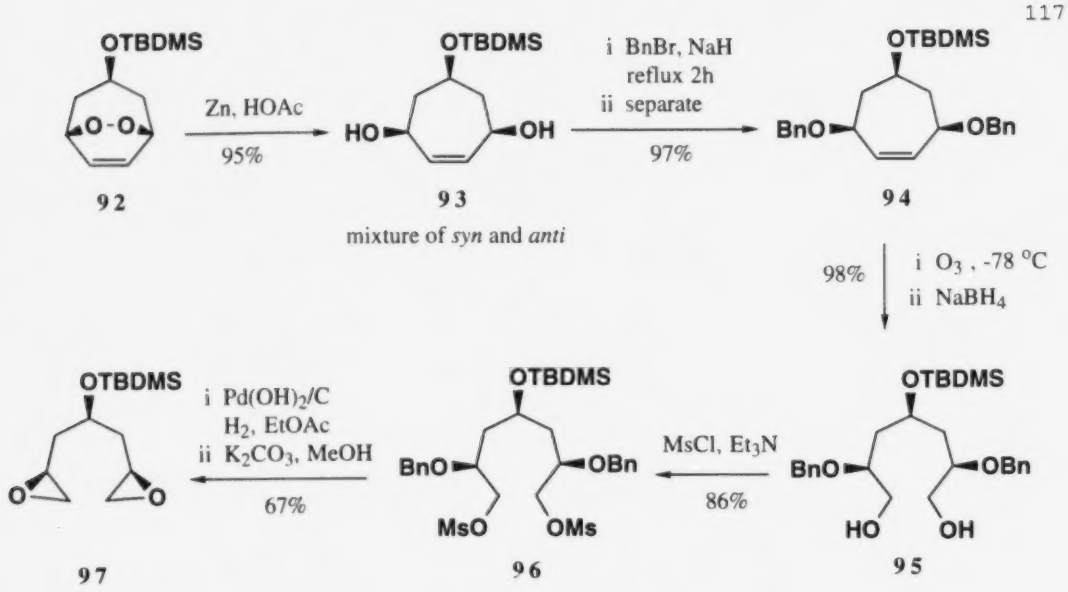


90 **91** **92**

Scheme 65

Alcohol **90** was protected without incident to give the silyl derivative **91**. Photochemical oxidation of the diene was the first major stumbling block encountered in the route.

Schreiber[81] reported that dichloromethane was used as the solvent. However, none of the desired product **92** was obtained using his conditions. When the method of Johnson and Senanayake[95] was tried, a better yield was obtained but still much lower than the published value. Johnson kindly informed us that the conditions specified in Scheme 65 (which are different from those in his publication) were critical, and that a minimal amount of porphyrin should be used. With this information, the problems in the photo-oxidation of the diene were solved. The above yield of the peroxide is the best we obtained. In later experiments it was found that partial purification of the peroxide **92** could be achieved by flash chromatography. However, the partially purified product always contained *ca.* 5% of the undesired isomer [^{1}H NMR estimate based on integration of the olefinic protons]. Complete separation of the isomers was achieved at a later stage (see Scheme 66).



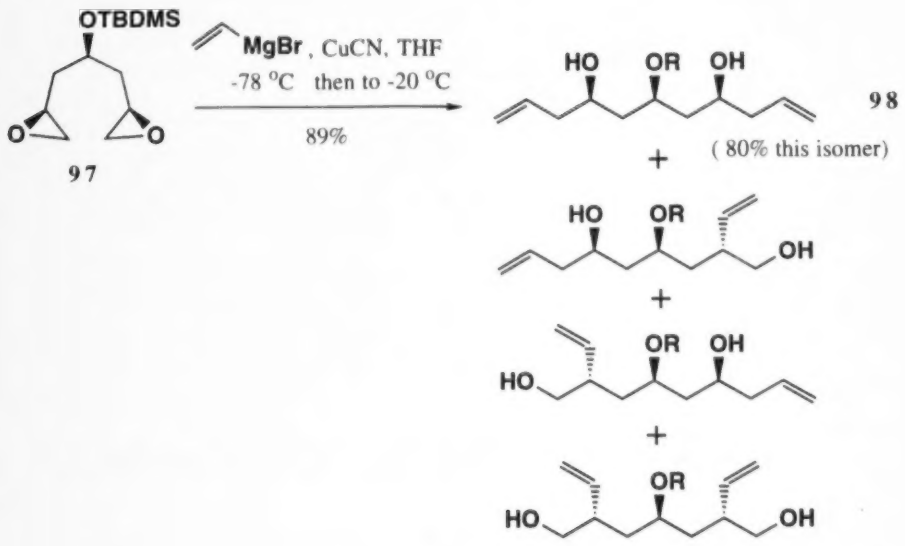
Scheme 66

Peroxide **92** was opened using zinc and acetic acid (Scheme 66), and the resulting diol **93** was protected as its bis (benzyl ether) **94**. It was found that refluxing the benzylation reaction mixture improved the yields over those reported by Schreiber (97% *versus* 80%).[81] The benzylation also allowed complete separation of any residual *anti* isomer that had not been removed after the photo-oxidation. Olefin **94** was cleaved by ozonolysis and reduced to diol **95**, using $NaBH_4$. The diol was then easily converted to bis mesylate **96**. However, it was found that compound **96** was not very stable. Therefore, it was usually just filtered through flash chromatography grade silica gel and then used promptly. Conversion of the bis mesylate to the bis epoxide **97** was very troublesome.

Scheme 66 reports a yield of 67% for the conversion of

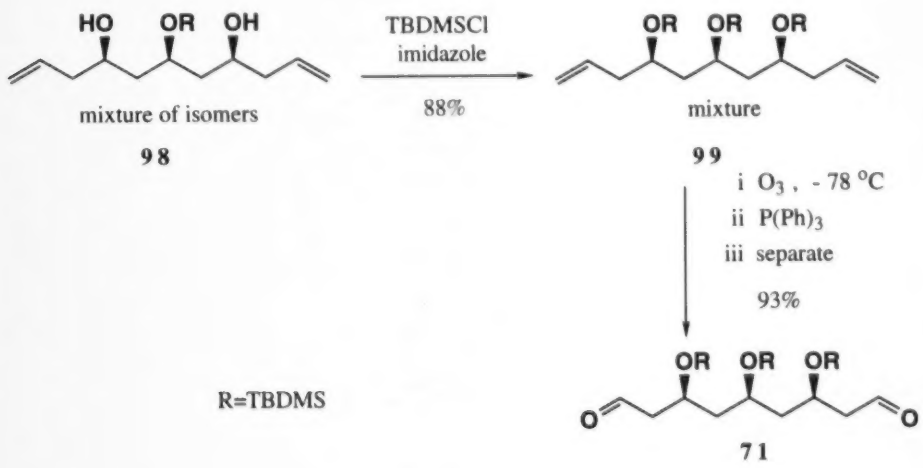
compound **96** to compound **97**. The experiment was done a number of times, and this yield is a typical value. On one occasion the literature yield[81] of 95% was reproduced; however, a three fold stoichiometric excess of the $Pd(OH)_2$ catalyst was required. The problem was narrowed down to the debenzylation step. Other hydrogenation catalysts were tried, such as Pt/C, Pd/C, and Rh/C, but these catalysts did not effect debenzylation. Compound **96** was also treated with Na and ammonia, but the desired bis epoxide **97** was again not obtained. We thought that the problem might involve the catalyst. $Pd(OH)_2$ is a very active debenzylation catalyst and is now commercially available. When these experiments were done it was necessary to prepare the catalyst, by the method of Hiskey and Northrop.[96] It is possible that the catalyst was not as active as desired, since better results were obtained with compound **96** when the catalyst was used while still wet. However, when test reactions of the catalyst on other substrates were run, benzyl groups were removed quantitatively. Nevertheless, if a large amount of the prepared catalyst was added in two portions, about an hour apart, a modest yield of the desired bis epoxide **97** could usually be produced.

Bis epoxide **97** was then converted into the bis aldehyde **71** described by Schreiber[81] (Schemes 67 and 68). The epoxide was opened using a vinyl cuprate to give mainly the diol **98**; however, the isomers could not be separated.



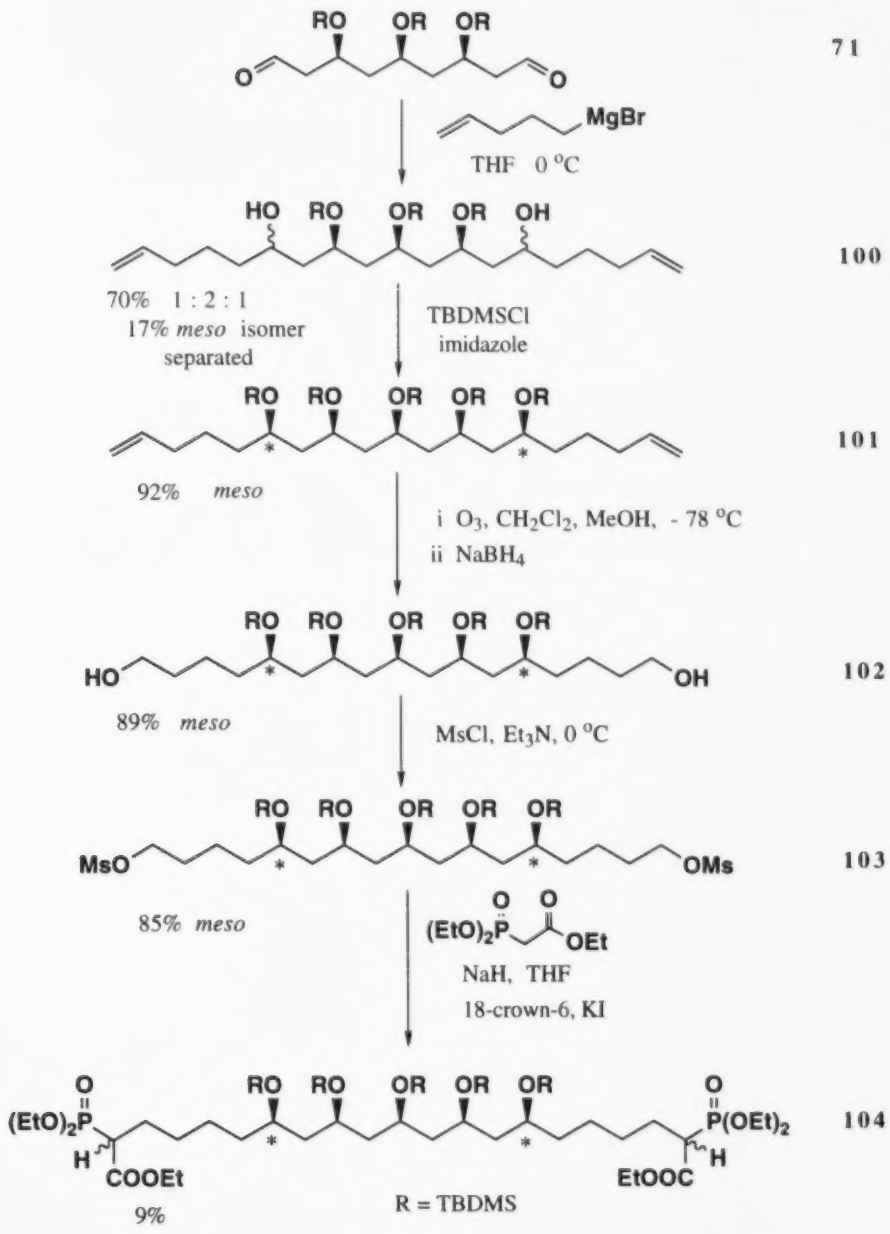
Scheme 67

The diol mixture was protected using TBDMSCl to give protected triol **99** as a mixture of isomers. Ozonolysis of



Scheme 68

99 then gave the desired bis aldehyde **71** and, at this stage, the isomers could be separated.

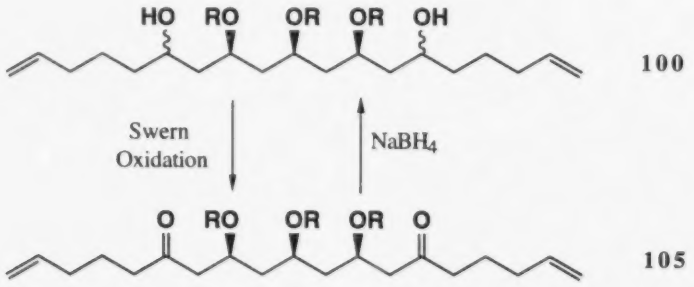


Scheme 69

Having the desired bis aldehyde **71** in hand, it was now necessary to convert it into the protected pentol bis

phosphonate **104**. This was done using the reactions illustrated in Scheme 69.

Bis aldehyde **71** was chain-extended at both ends, using the Grignard reagent derived from 5-bromopentene. The reaction gave a statistical mixture of isomers [1 (*meso*): 2 (*d,l*): 1 (*meso*)] labeled as compound **100**. It was possible to separate one of the *meso* isomers, and all subsequent reactions were done on this diastereoisomer. The configuration at the starred carbons (see **101**) was not established, and the configuration of the hydroxyl groups at these carbons has been arbitrarily drawn *syn* to the others. (An asterisk is used to denote that the configuration of the asymmetric center is unknown in all the following structures.) A recycling procedure was developed for the other diastereoisomers, as shown in Scheme 70. The mixture



Scheme 70

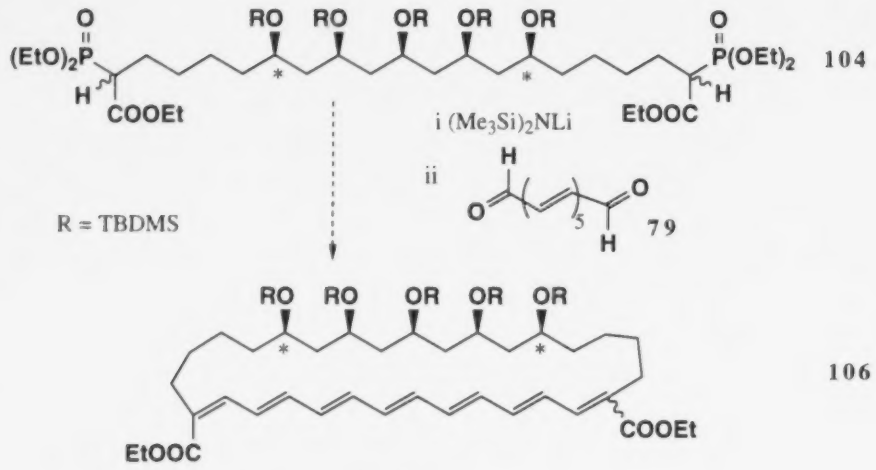
of diols **100** was subjected to Swern oxidation to give bis ketone **105**, which was then reduced to a statistical mixture of diastereoisomers **100**. The recycling procedure could be used only two or three times on any batch of material because

the basic conditions of the reduction caused loss of some of the silicon protecting groups, making separation of the pure *meso* diastereoisomer difficult.

The separated *meso* **100** was protected using TBDMSCl to give the penta(TBDMS)-protected compound **101** in 92% yield. Ozonolysis of **101**, followed by reduction with $NaBH_4$, gave diol **102**. It was now necessary to convert the hydroxyl groups to leaving groups, and this was done by making bis mesylate **103**, using standard conditions.

It seemed that the desired bis phosphonate **104** would now be accessible, but problems arose in the alkylation, using triethyl phosphonoacetate. Only a very low yield (9%) of **104** was obtained and it was always contaminated with triethyl phosphonoacetate. The two compounds were chromatographically inseparable and, when Kugelrohr distillation was tried, the desired compound decomposed. When potassium hydride was used as the base, the same yield was obtained. Both HMPA and 18-crown-6 were added to make the anion more nucleophilic, but there was no improvement in yield. A mixture of NaH, triethyl phosphonoacrylate, DMSO and KI (catalytic) was also tried, but again the yield was not improved, although the product was purer.

An attempt to carry out the macrocyclization was made using impure **104** (contaminated with triethyl phosphonoacetate) in the hope that the desired macrocyclic material **106** would be formed (Scheme 71).



Scheme 71

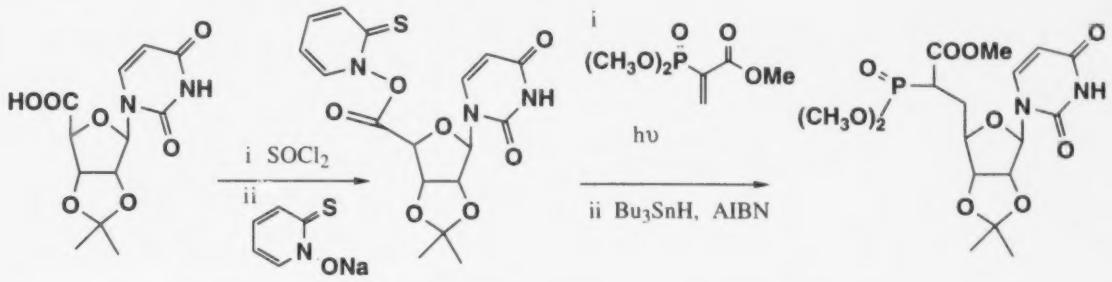
The reaction mixture was purified by preparative TLC but only a very small amount (*ca.* 2-3 mg) of what is thought to be the isomers of compound **106** was obtained. The ^{1}H NMR spectrum was consistent with the desired macrocyclic structures but the integration was unsatisfactory. The fragmentation pattern in the mass spectrum was not understandable and no molecular ion was observed. After the isomers were treated with fluoride ion, to remove the protecting groups, the mass spectrum of each compound showed peaks at 646 (deprotected product, M = $C_{37}H_{58}O_9$), 628 (M - H_2O) and 601 (M - OEt). The compound decomposed before more measurements could be made.

Since we felt that the macrocyclization might have worked, a better method for preparation of compound **104** or a compound of similar structure was needed, and we decided to adapt a method developed by Barton and co-workers,[97] as

described in the next section.

V.4. Proposed Method for the Introduction of Phosphonate Groups

The following reaction (Scheme 72) developed by Barton and co-workers[97] appeared to suit our requirements.



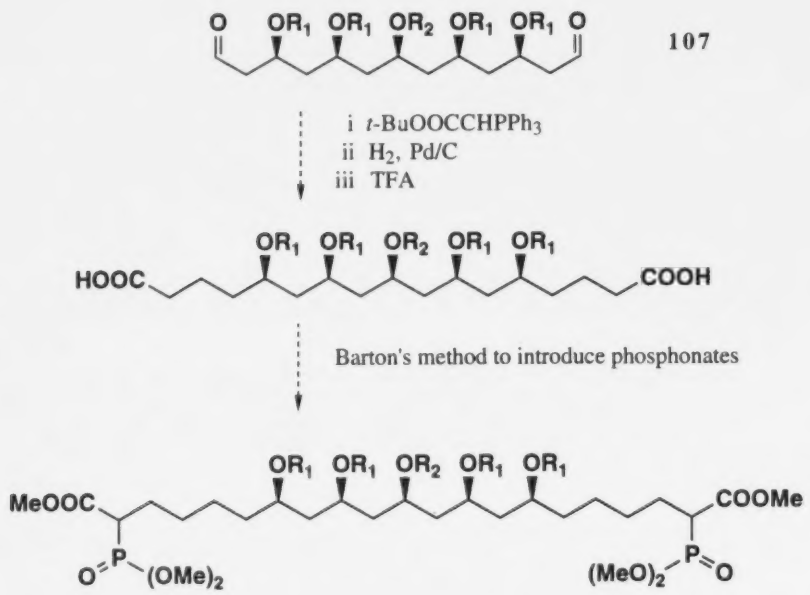
Scheme 72

The overall yield in this type of radical Michael addition was reported to be 70-94% for a variety of substrates. We noted that the acrylate reagent is volatile and thus can be removed easily. This fact was important because we had previously found difficulties in chromatographic separation of phosphonate reagents from our phosphonated products. Thus, this type of radical process seemed to be ideal for attaching phosphonates onto the ends of a carbon chain.

We needed, therefore, to prepare suitable polyhydroxy compounds that would allow the Barton method to be used.

A literature search identified compound **107** (see Scheme 73), which would give the appropriate length of protected

1,3-polyol, as a substrate, and the planned sequence is summarized in Scheme 73.

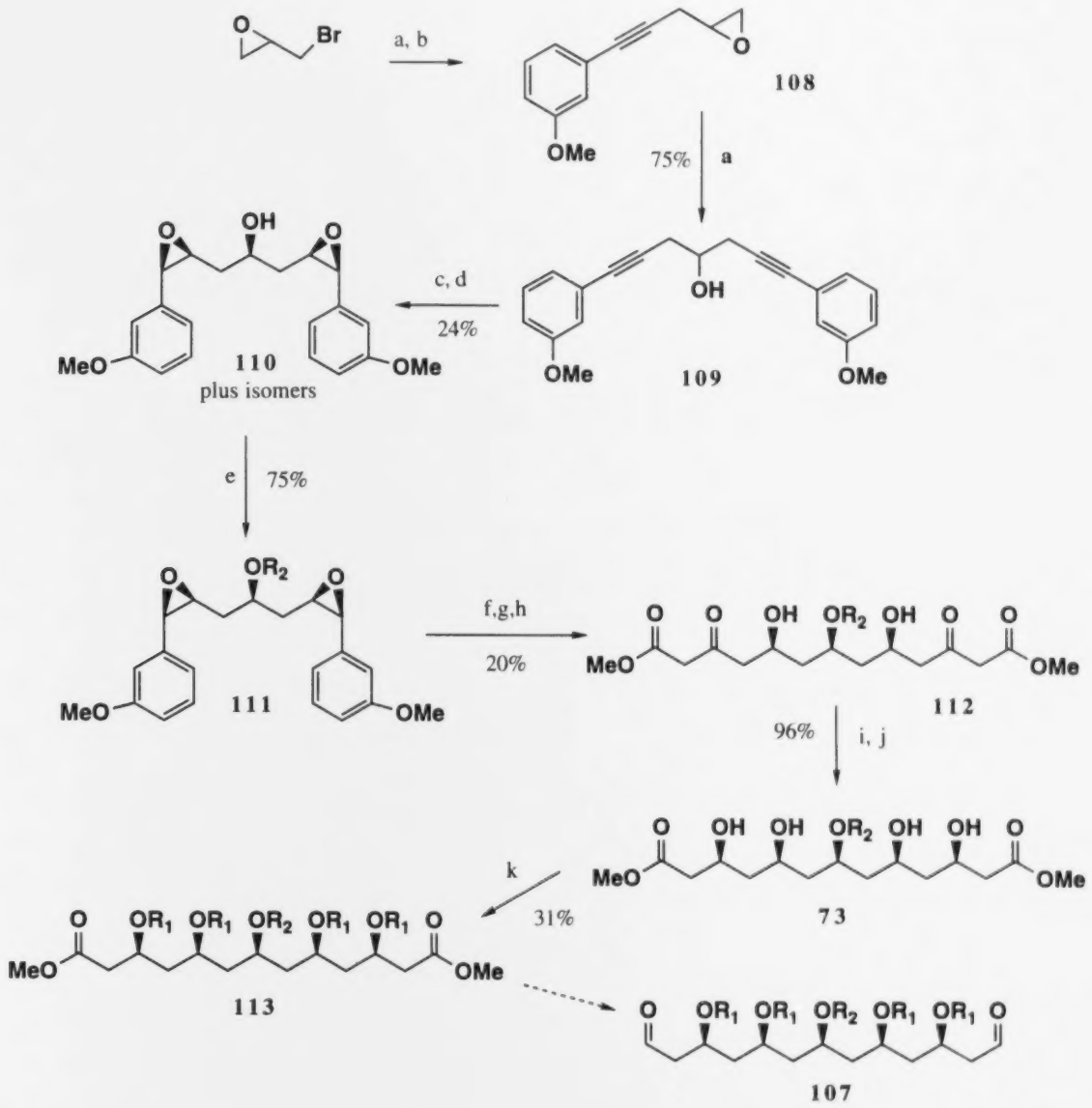


Scheme 73

Wang and Dechênes had previously prepared compound **107**,[84] and their route was examined (Scheme 74). However, there were difficulties in repeating the experiments almost from the beginning.

The authors were contacted and additional information was obtained in the form of copies of the notebook pages. The experimental details were sketchy and in some cases the data in the supplementary material conflicted with the published method. It was important that freshly distilled boron trifluoride etherate be used for the addition of lithium (3-methoxyphenyl)acetylide to epibromohydrin. Also,

the semireduction of the alkynes to the *Z* olefins requires addition of ethylenediamine to poison the catalyst.



a) lithium (3-methoxyphenyl)acetylide, BF_3-OEt_2 b) K_2CO_3, MeOH c) Ni_2B, H_2, EtOH, ethylene diamine d) VO(acac)$_2$, *t*-BuOOH e) TIPSOTf, Et_3N f) Li, NH_3 g) O_3 h) PhP_3 i) Et_2BOMe, -78°C j) $NaBH_4$ k) TBDMS-OTf, E_3N

R_1 = TBDMS
R_2 = TIPS

Scheme 74

In our hands, the semireduction was difficult and the olefin was often over reduced to the alkane. The reaction was monitored by ^{1}H NMR spectroscopy and the reaction time was quite variable. Best results were obtained when the reaction was stopped at a stage when the ^{1}H NMR spectrum indicated about 50% completion.

For the Sharpless epoxidation to generate bis epoxide **110**, $VO(acac)_2$ was used instead of $VO(O\textit{i}\text{-}Pr)_3$. The desired epoxide was produced, but as a 9:1 mixture of the desired compound to other possible isomers (^{1}H NMR). The selectivity was lower than that reported for $VO(O\textit{i}\text{-}Pr)_3$, which gave a 15:1 isomer ratio. The authors reported that the isomers could be separated, but we found this to be impossible, not only with the chromatography system given in the supplementary material but also with many other systems. It was decided to carry the isomers through the following steps in the hope that they could be separated at a later stage.

The hydroxyl group of **110** was protected using the TIPSOTf. The silyl protected analog of **110**, compound **111**, and subsequent compounds in the series were quite acid-sensitive. The aromatic rings of **111** were reduced by Birch reduction, the method of Evans[69] being found to work best. The crude Birch reduction product was immediately ozonized to give bis(ketoester) **112**. Dimethyl sulfide was better than triphenylphosphine for the reduction of the ozonides because it allowed easier purification of the product. Compound **112** appeared to be quite pure, as judged by both ^{1}H and ^{13}C NMR

spectra. This was surprising because it meant that only one product was produced starting from a mixture of four compounds. Consequently, we were not certain that **112** was indeed as pure as the spectra would indicate. The bis-(ketoester) **112** was stereoselectively reduced to **73**. The ^{13}C NMR spectrum (125 MHz) of compound **73** confirmed our suspicions that other isomers were present, as evidenced by several small signals at similar shifts to those of the desired compound.

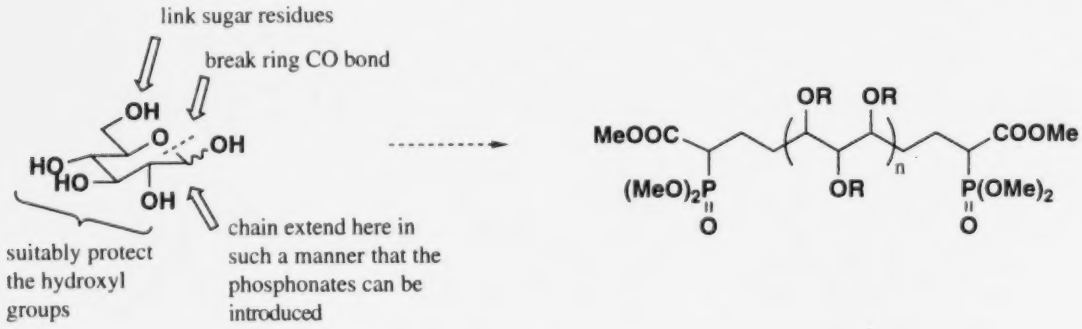
Compound **73** was protected in low yield (31%), using TBDMSOTf, to give compound **113**. Compound **113** was extremely unstable and decomposed upon attempted purification.

We were eventually forced to abandon this route because we could not separate the isomers, and because of the instability of some of the compounds in the sequence. Although we appreciate that the fault may lie with us, the fact is, we had lost confidence in the published route. We clearly needed a new approach to the problem of generating a polyhydroxy bridge, and we turned now to carbohydrates because they offered a ready source of polyhydroxylated compounds that, in principle, could be used to construct a suitable polyhydroxy chain.

V.5. General Comments on the Synthesis of Polyhydroxy Bis phosphonates from Carbohydrates

To use carbohydrates in the present context, a number of synthetic tasks need to be addressed (Scheme 75). The sugar

must be suitably protected, the ring of the sugar needs to be opened and the carbon chain extended in such a way that Barton's method for introduction of the phosphonates can be used. Finally, two sugar residues must be linked at the C-6 position.



Scheme 75

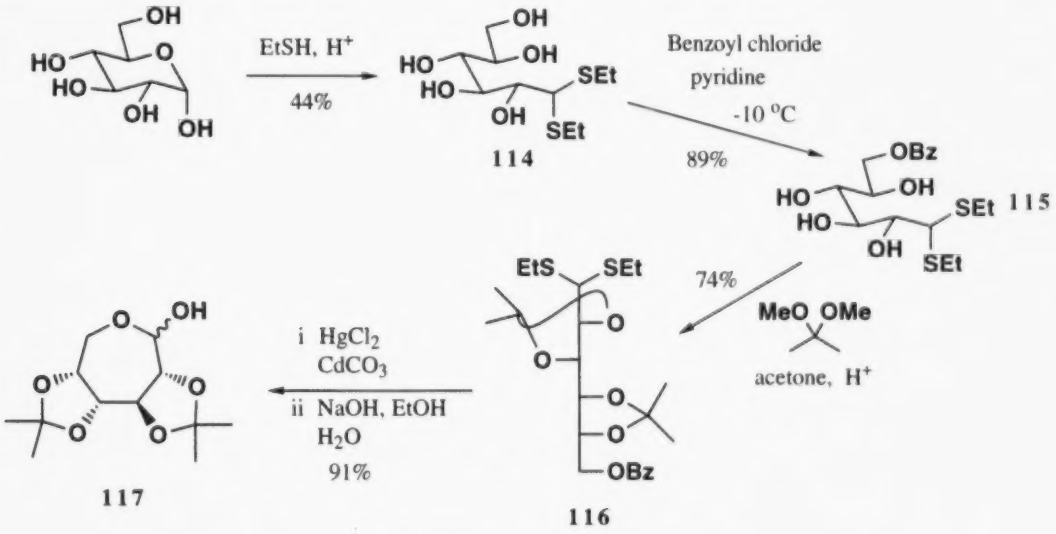
Since many stereochemical possibilities and chain lengths of carbohydrates are available, one should be able to generate a library of structures for biological evaluation.

It was felt that the best approach was to link the sugars first and then to chain-extend the resulting material. Most of the methods tried follow this plan; however, the routes also allow chain extension before linking of the monosaccharides.

V.6. Development of Coupling Procedure for Disaccharides

An additional problem encountered in this project is that the polyene system of the macrocycle is chemically

sensitive and this fact limits the types of protecting groups available for use in other parts of the target. Nicolaou and co-workers[54] had demonstrated that the isopropylidene group could be removed under conditions that did not damage the polyene system. A literature search revealed that Ng and Stevens[98] had published work in which the 2,3- and 4,5-hydroxyls of D-glucose had been protected by isopropylidene groups. The reaction sequence shown in Scheme 76 was repeated to give **117** with the desired isopropylidene protection pattern.

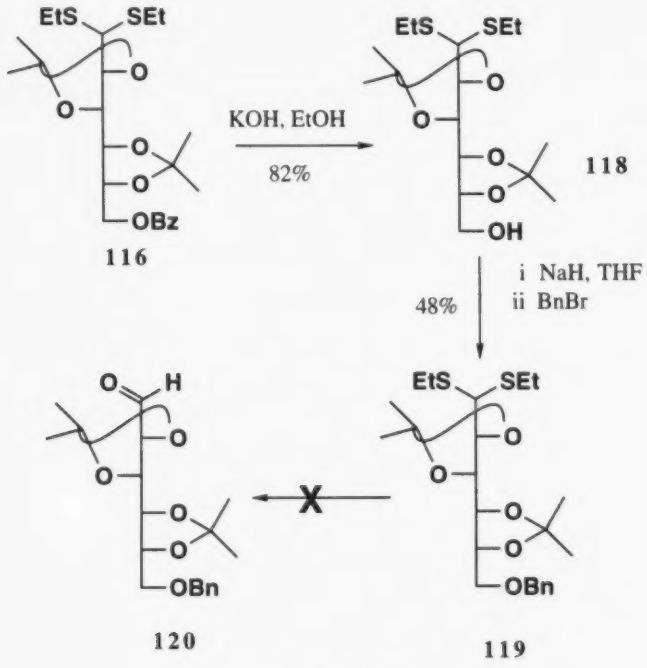


Scheme 76

The route worked well and large amounts of compounds **116** and **117** became available. These two compounds appeared to be ideally constituted for our purposes as the C-1 and C-6 positions were differentially protected and could be

manipulated individually. We considered first the possibility of using a McMurry coupling to join the sugars, and this meant that an aldehyde function was desired at one terminus. Sugars already possess an aldehyde at C-1, and so an attempt was made to protect the C-6 hydroxyl and then free the aldehyde.

Starting from compound **116**, the sequence of Scheme 77 was carried out. The benzoate group of **116** was removed with

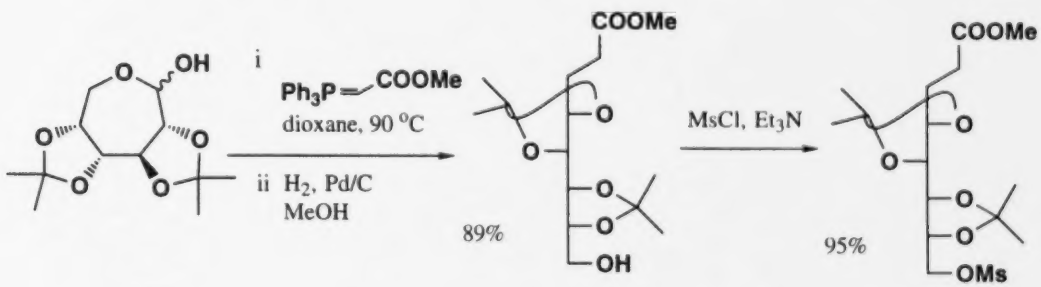


Scheme 77

potassium hydroxide in 95% ethanol. Although the ^{1}H NMR, MS and FT-IR spectra of compound **118** were satisfactory, the ^{13}C NMR spectrum indicated the presence of some impurities. These could be due to a small amount of isopropylidene

migration. Alcohol **118** was then benzylated using sodium hydride in THF with benzyl bromide to give a low yield of **119**. Again, the ^{13}C NMR spectrum indicated increased amounts of a contaminant, but it was thought to be less than 15%, and so the next step was tried. Removal of the dithioacetal protecting group was tried under a variety of conditions: $HgCl_2$, $CdCO_3$;[98] isoamyl nitrite;[99] $HgCl_2$, HgO;[100] $AgNO_3$, MeCN;[101] I_2, $NaHCO_3$;[102] $Tl(NO_3)_3$;[103] CAN, MeCN; NBS, acetone;[104] and MCPBA.[105] However, none of these reagents afforded the desired aldehyde **120** and all of them caused decomposition, except for $AgNO_3$, and in that case the starting material **119** was recovered.

Since deprotection of dithioacetal **119** could not be accomplished, a Wittig reaction was tried (see Scheme 78) on the isopropylidene protected reducing sugar **117**. The Wittig



117 **121** **122**

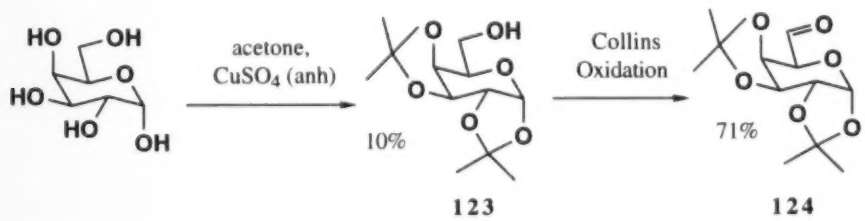
Scheme 78

reaction worked very well and the resulting α,β-unsaturated ester was hydrogenated to ester **121**. Attempts were then made to oxidize the C-8 hydroxyl of **121**, as we needed an aldehyde

for the planned McMurry coupling. However, the conditions of both Swern and Collins oxidation caused decomposition.

Since the aldehyde could not be obtained it was thought that an ether linkage between the sugar residues could be used. To this end, mesylate **122** was prepared, but attempts to use it to alkylate the sodium salt of **121** were unsuccessful. Possibly, enolization of the ester in compounds **121** or **122** interferes with the desired reaction.

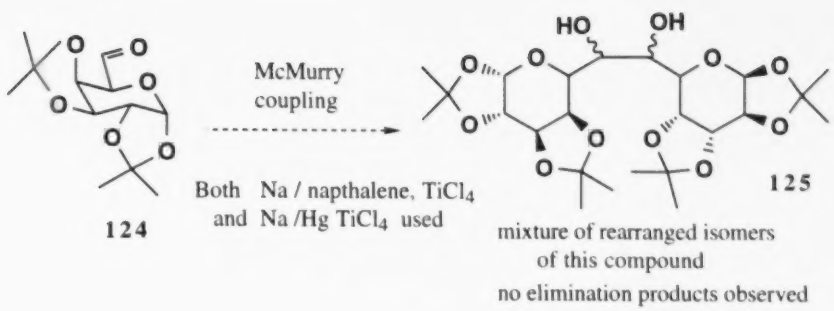
While seeking methods to oxidize alcohol **121** to the aldehyde, the procedure of Lemieux and co-workers,[106] which had been applied to a D-galactose derivative (Scheme 79), was found, and it appeared that the product (**124**) would be suitable for our purposes. Consequently, compound **124** was



123 **124**

Scheme 79

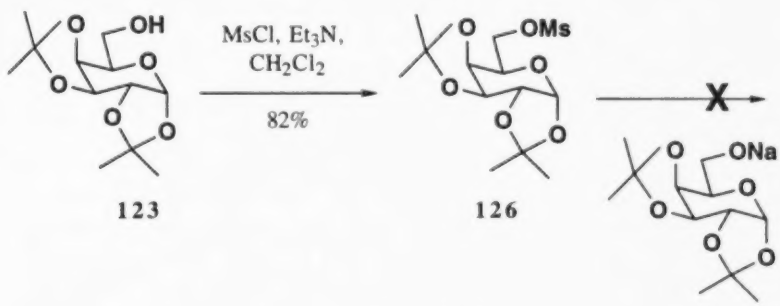
prepared and the McMurry coupling reaction was tried. Both Na/naphthalene, $TiCl_4$ and the Na/Hg/$TiCl_4$ procedures that had been developed in this research group[107,108] were examined. Unfortunately, the coupling procedure did not work in the desired sense, and gave many products, which were isomers of



Scheme 80

compound **125** (Scheme 80). The mixture of isomers **125** did not contain only the diol shown, because the titanium had catalyzed rearrangement of at least one of the isopropylidene protecting groups.

An attempt was next made to join two protected galactose residues, based on **123**, via an ether linkage (Scheme 81).



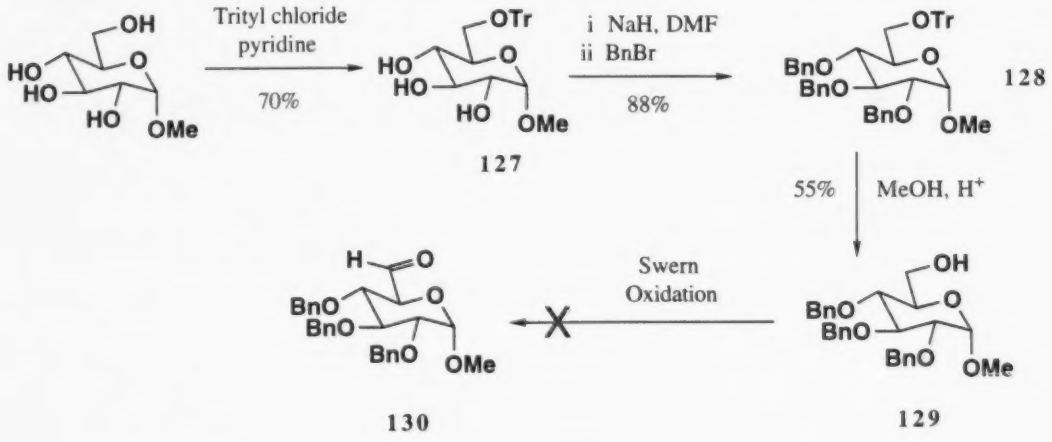
Scheme 81

The mesylate **126** was made easily, but all attempts to use it to alkylate the sodium salt of alcohol **123** were unsuccessful.

Since the isopropylidene-protected carbohydrates had undergone the carbonyl coupling step in the McMurry reaction but further elimination had probably been thwarted by

migration of isopropylidene groups, a more persistent protecting group, such as benzyl, was now considered.

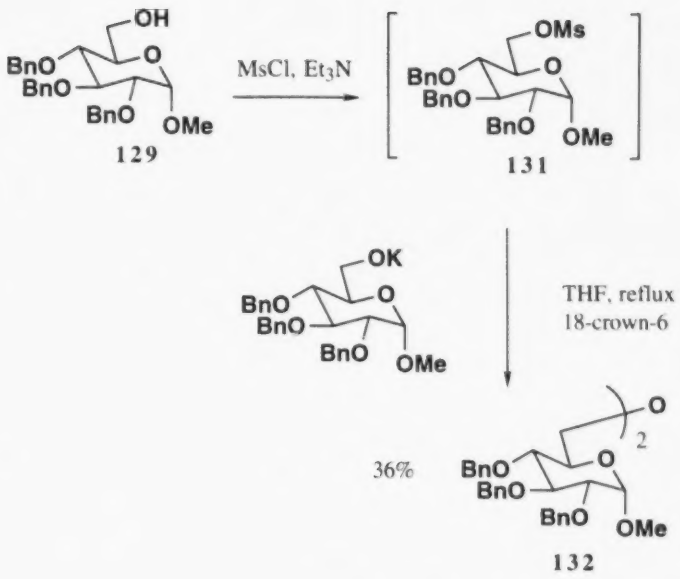
Bernet and Vasella[109] had prepared (Scheme 82) a benzyl-protected D-glucose derivative (**129**) with the C-6 hydroxyl free. Preparation of compound **129** was straightforward, and



Scheme 82

attempts were made to oxidize it to aldehyde **130**. However, aldehyde **130** was obtained in a form that appeared to be a hydrate, and, therefore, was not suitable for McMurry coupling.

Using compound **129**, another attempt was made to prepare



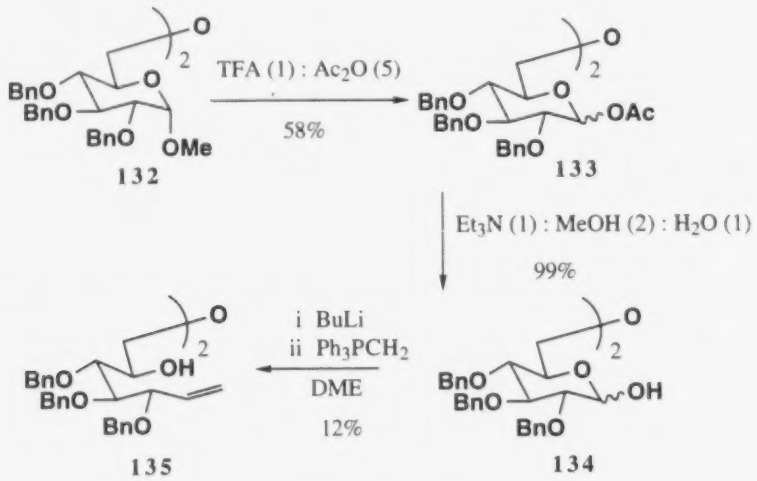
Scheme 83

an ether-linked 6',6-disaccharide, as shown in Scheme 83. With the sodium salt of compound **129** no alkylation was observed, and the same result was obtained when the C-6 trimethylsilyl ether of **129** was made and treated with CsF in the presence of mesylate **131**. Different solvents were tried, such as DMSO, DMF and dioxane; however, the only experiment which gave compound **132** involved the use of KH (5 to 7 equivalents) in what amounted to a saturated solution of 7 equivalents of 18-crown-6 in THF. 6',6-Anhydro sugars are not well-known, and only two examples have been reported.[85] Formation of **132** solved one of the synthetic problems, i.e. the linking of the two sugar residues.

V.7. Development of Chain Extension Methods and Application to Disaccharides

Having a supply of disaccharide **132** in hand, the next

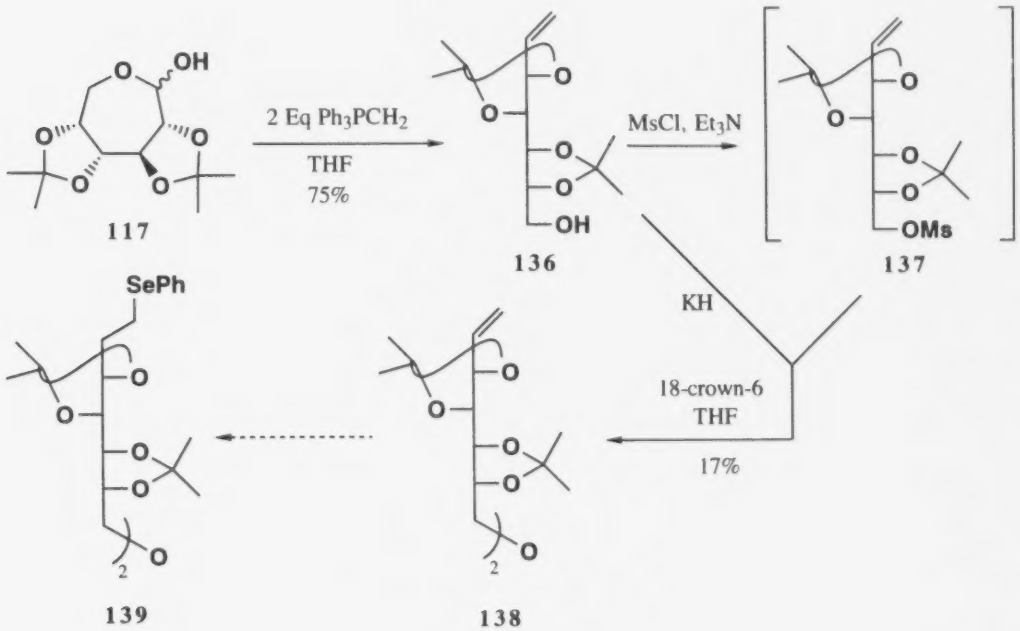
step was to extend the chain at the anomeric centers. We first tried Wittig chemistry, as summarized in Scheme 84.



Scheme 84

Our plan was to protect the anomeric centers by Wittig olefination and then to protect the C-5 hydroxyl of compound **135**. This would allow ozonolysis of the olefin followed by chain elongation. An acetolysis procedure was developed, based on work by Krepinski and co-workers,[110] to give compound **133** as a mixture of anomers. The procedure worked well on a small scale (<100 mg) but yields were low on larger scales (*ca.* 1 g). We found that cooling (0 °C) and slow addition of TFA allowed the reaction to be run on about 500 mg with acceptable yields (50 - 80%). The amount of TFA is critical, and addition of TFA should be stopped at the point that the solution color starts to deepen. The acetate group was removed by hydrolysis [Et_3N (1):MeOH (2):H_2O (1)][111] to afford

the free reducing sugar **134**. In practice, the acetolysis and hydrolysis steps were usually run without isolation of the moisture-sensitive bis acetate **133**. Wittig chain extension at the anomeric centers did work, but with disappointing results. A yield of only 12% of the doubly chain-extended disaccharide **135** was obtained. The reaction conditions were varied and it was found that DME was the only solvent which gave any of the desired material (THF and DMF were also tried). The route was not pursued further because of the low yields.



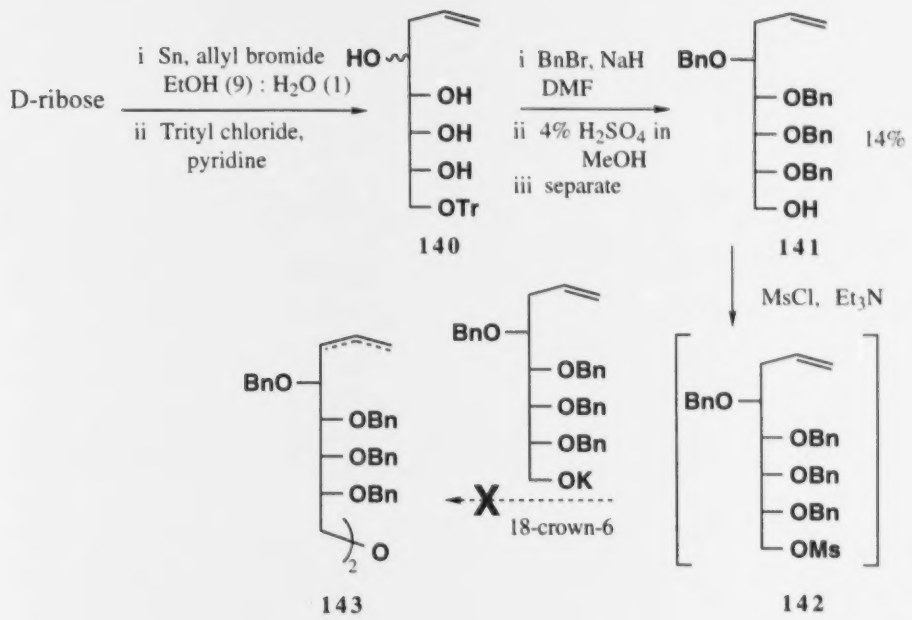
Scheme 85

Since the use of Wittig olefination at the anomeric center was convenient, the reaction was repeated on the isopropylidene-protected monosaccharide **117**. It was felt that the yields might be increased if the olefination were

carried out *before* coupling of the sugar residues (see Scheme 85).

Wittig reaction with compound **117** turned out to be straightforward, and the resulting olefin (**136**) was converted to the symmetrical disaccharide **138** by first making the mesylate **137** and then using the linking procedure previously described. Since we needed to generate a radical at the terminus of the olefin (chain terminus), we decided to try to hydroborate the olefin and then to introduce a phenylseleno group, as in compound **139**. Olefin **138** was treated with BH_3-SMe_2 complex and then with NaOOH to give a mixture of unstable alcohols. The reaction was tried again, and the crude hydroboration-oxidation product was treated with PhSeCN and Bu_3P to afford what was we take to be phenylselenide **139**. The compound could not be characterized, but spectra indicated that it was a mixture containing mainly the terminal PhSe-substituted disaccharides contaminated with some material in which the PhSe had been introduced at the secondary carbon. The isomers were inseparable in all chromatography systems tried and so this route was not pursued further.

Barbier coupling of allyl bromide and sugars had been reported,[90] and a potential route based on this methodology is illustrated in Scheme 86.



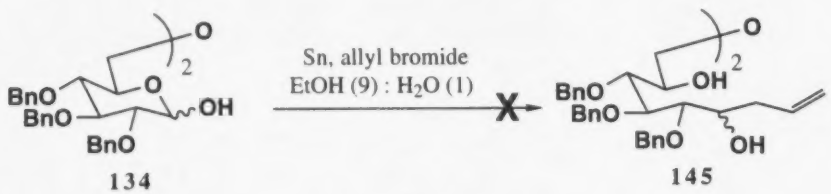
Scheme 86

Treatment of D-ribose with tin and allyl bromide afforded a mixture of C-5 isomers (corresponding to the unprotected form of **140**). The mixture was reported to be separable by peracetylation and chromatography and, although we found that this procedure worked on a small scale, the separation was unsuccessful in large scale experiments. Therefore, the mixture of isomers from the Barbier coupling was tritylated to afford compounds **140**. The isomers could still not be separated, and so the mixture was benzylated and the trityl group was removed, to afford **141**, still as a mixture of isomers. Repeated chromatography of the mixture allowed isolation of the major *altro*-isomer (as in **141**). Whitesides had shown that the major isomer produced in the Barbier coupling was the *altro* product,[90] and we relied on his

stereochemical assignment for our product.

When we tried coupling between **141** and its potassium salt in order to obtain disaccharide **143**, the reaction may have worked, but the double bond migrated to the 2-position of the chain in *ca.* 50% of the material. The material could not be satisfactorily characterized because the isomers were inseparable, and so this route had to be abandoned.

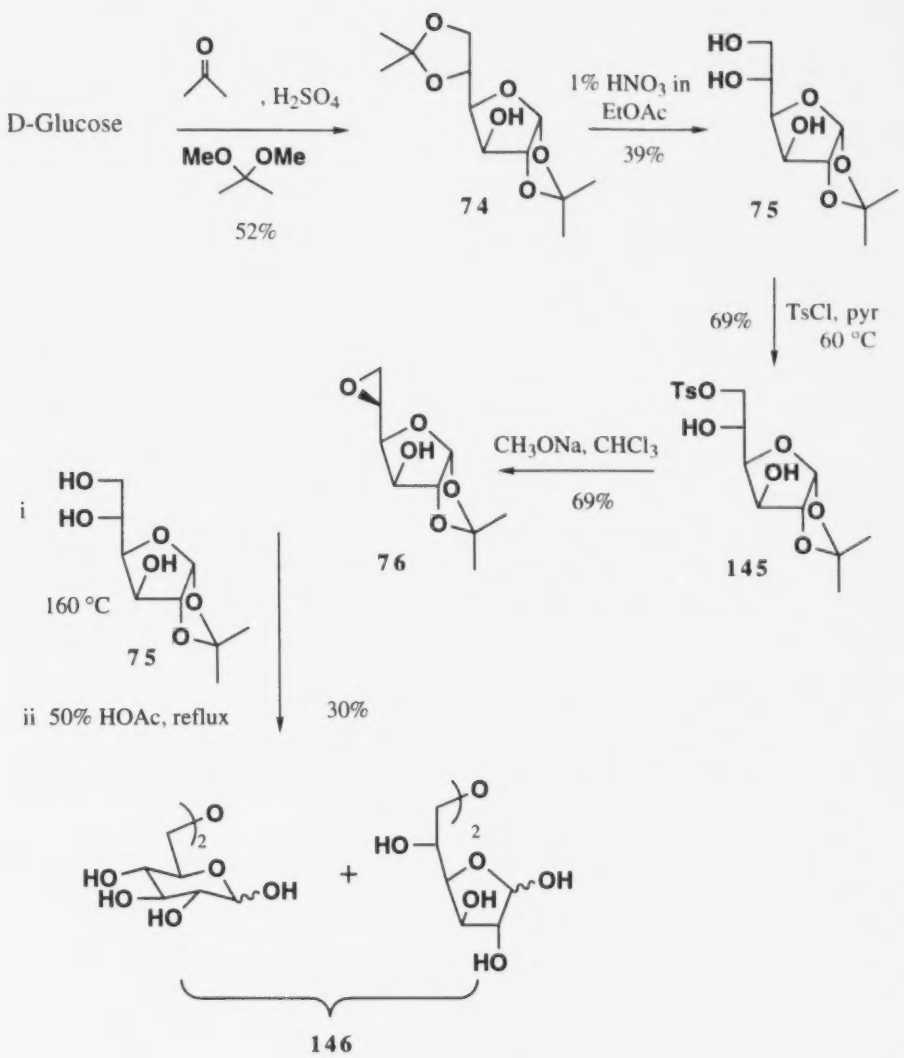
It was thought that Whitesides' allylation could be applied to disaccharide **134**, as summarized in Scheme 87.



134 145

Scheme 87

However, the reaction did not work and only the starting disaccharide **134** was recovered. We felt that a free C-2

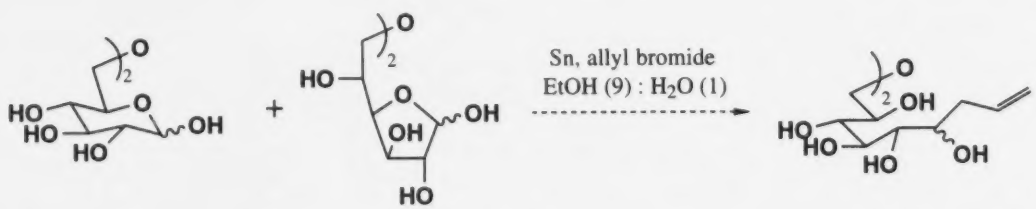


Scheme 88

hydroxyl group was probably necessary to provide a binding site for the tin and assist delivery of the allyl anion to the anomeric center. Accordingly, it was decided to prepare disaccharides **146**, as shown in Scheme 88. The material had actually been reported by Whistler and Frowein[85] and is one of the two reported examples of 6',6-disaccharides.

The reaction sequence was repeated easily, and it was found that tosylate **145** was obtained in higher yields if purification was done by flash chromatography rather than by crystallization. The disaccharide was difficult to characterize because there are 12 possible isomers produced in the reaction. The spectra were consistent with the expected gross structures and FAB MS measurements indicated material of the expected molecular weight, as well as higher molecular weight components.

The mixture of isomers (**146**), which always contained a trace of acetic acid, was treated under Whitesides' conditions,[90] and the chain extension was accomplished, to afford what is believed to be compounds **147**, as shown in Scheme 89. The chain-extended compound was produced as a



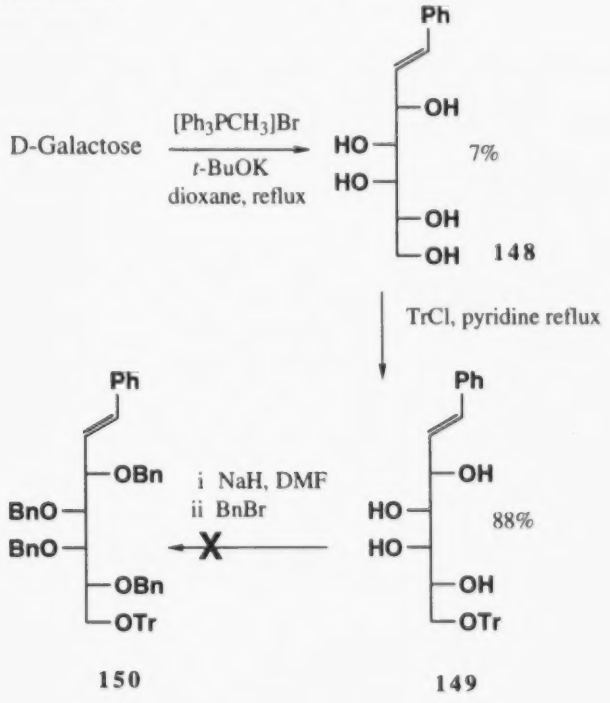
146 **147**

Scheme 89

mixture of four diastereoisomers, and was contaminated with a large amount of tin that was bound to the product. A suitable derivative that allowed purification of one of the isomers could not be found. Since the diastereoisomers could

also not be separated, it was decided to investigate other methods for chain extension at anomeric centers.

A paper by Sandhoff and co-workers[89] demonstrated that Wittig reactions could be done on unprotected sugars using stabilized ylides. It was decided to try this approach on a monosaccharide (Scheme 90) so that, after protection, the material could be coupled to form a 6',6-disaccharide. At that point, it was our intention to ozonize the carbon-carbon double bonds so as to generate terminal aldehydes. These aldehyde groups would serve as the starting points for further elaboration.

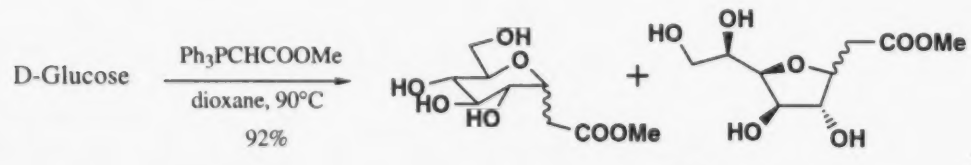


Scheme 90

The yield (7%) of the anomeric-protected sugar **148** was

significantly lower than the yield given in the paper (70%). We found that the reported purification procedure did not work well because traces of butoxide in the reaction mixture caused decomposition of the product. However, neutralization of the reaction mixture allowed the desired compound to be isolated (7%). The terminal hydroxyl group was protected, to give **149**, and several attempts were then made to protect the remaining hydroxyl groups as benzyl ethers. Such groups would be stable to the conditions of the coupling procedure. To our disappointment, sodium hydride used in the protection step caused decomposition of the substrate and no benzyl-protected sugar **150** was ever isolated.

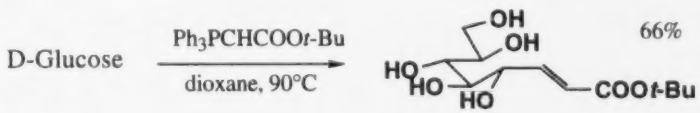
A paper by Fraser-Reid and co-workers[112] indicated that (carbomethoxymethylene)triphenylphosphorane could be used for chain extension at the anomeric center. Some Michael addition occurred, but some of the product could be isolated in the open chain form. The Fraser-Reid conditions did not work on our substrate or on D-glucose but, after modification of the procedure, we were able to observe Wittig olefination, although this was followed by Michael addition to give a mixture of compounds (**151**) (Scheme 91).



151

Scheme 91

The reaction shown in Scheme 91 was tried ten times and in every case a high yield of the *C*-glycoside was formed. The open chain form was often observed (olefin signals in the ^{1}H NMR spectrum) immediately after reaction but, upon standing in water during the purification procedure, the compound formed the *C*-glycoside. The rate of Michael addition appeared slightly faster in basic solutions. We wondered if the ease of Michael addition was at all sensitive to the nature of the ester, and so the reaction was retried using [carbo(*t*-butyloxy)methylene]triphenylphosphorane (Scheme 92).



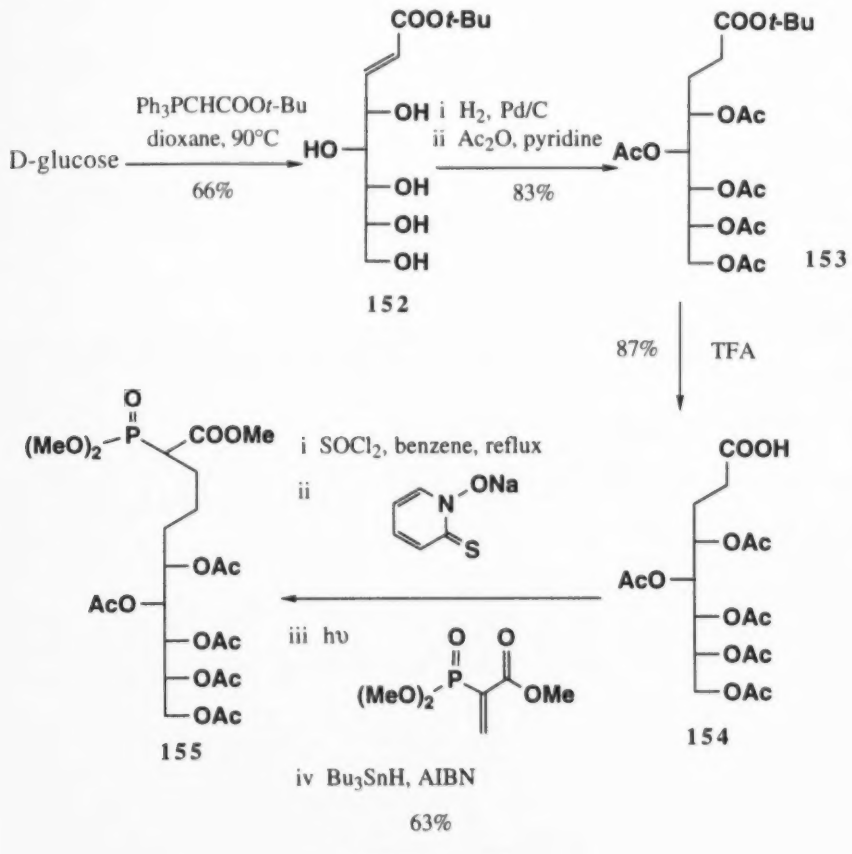
152

Scheme 92

A very different result was now observed: the open form of the chain-extended sugar **152** was the only product found, and the material had exclusively the *E* geometry. The crude product was isolated in about 90% yield, but was contaminated with traces of Ph_3PO. Purification by recrystallization from methanol gave **152** in 66% yield.

With a chain-extension method available, that would generate suitable functionality for introduction of a phosphonate unit by Barton's method,[97] now in hand, we decided to practice the complete sequence – chain extension and

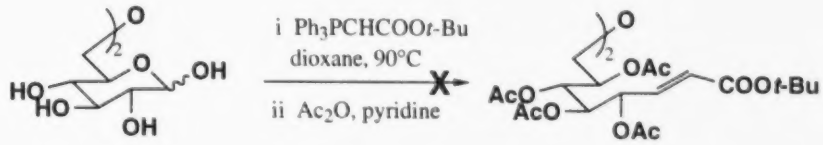
introduction of the phosphonate – on D-glucose (Scheme 93).



Scheme 93

The reaction sequence proceeded smoothly. Acetylation to give compound **153** was best effected using a 2:1 mixture of pyridine and acetic anhydride. The undesired sulfide-linked aromatic product of the free radical Michael reaction was reduced to the alkane (to give **155**) with Bu_3SnH, and the desired compound (**155**) was obtained in pure form in acceptable yields. These encouraging observations led us to try the method on disaccharides.

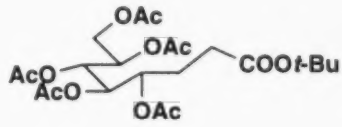
The first disaccharide used was the unprotected glucose-derived compound **146** (Scheme 94). The reaction produced a



146

Scheme 94

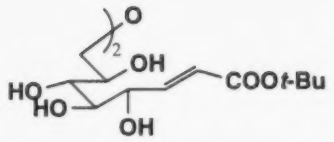
variety of products and the only identifiable one was compound **153** (which we had made previously), evidently formed from monomeric material still present in our sample of disaccharide.



153

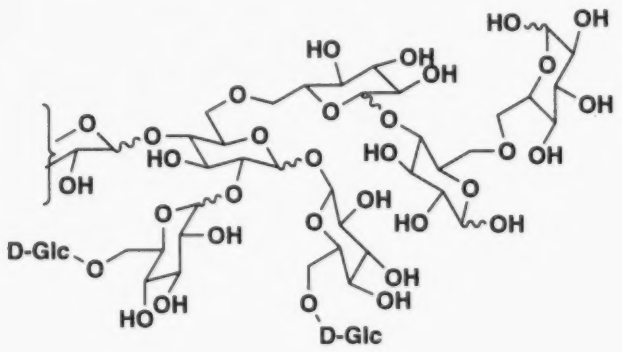
We thought that the apparent lack of reactivity of the disaccharide might be due to insolubility in dioxane, and so the experiment was repeated using a 1:1 mixture of DMF and dioxane, but again only the chain extended monosaccharide **153** was isolated.

The mass spectral data for compound **146** indicated that there were components of the mixture with masses higher than the expected molecular weight of 342. We also noted that the



156

^{1}H NMR spectra of the crude reaction mixtures from attempts to make the chain-extended disaccharide **156** showed broad peaks in the region where the anomeric hydrogens were expected to give signals. The ^{1}H NMR spectra always showed an excess, relative to the amount of olefinic and *t*-butyl absorptions, of species containing **H**-C(OH)R_2. These facts indicate that the structure assignment by Whistler and Frowein[85] is probably incorrect, and the sample of compound **146** is most likely a complex mixture of D-glucose, compound **146**, and higher polysaccharides (**157**). The conditions for removal of the acetic acid could well lead to formation of this type of mixture.

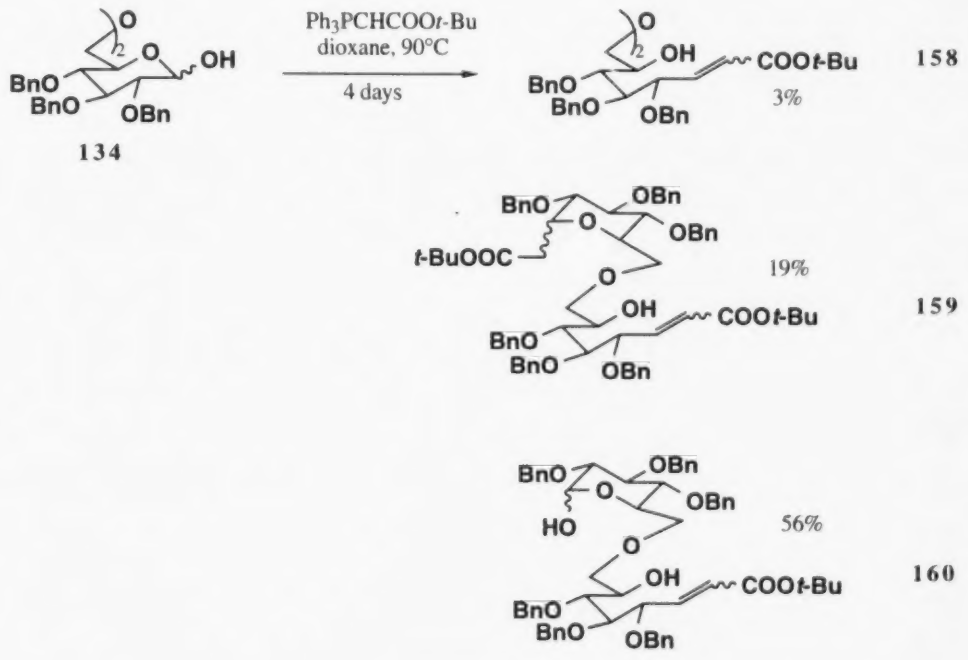


157

The presence of higher order polysaccharides (**157**) would also explain the need for unusually harsh conditions [Ac_2O,

NaOAc, 150 °C] in the peracetylation – evidently acetic acid in the reaction mixture served to cause fracture of the acetal linkages in the oligosaccharides. Similarly, our problems in attempts to allylate[90] compound **146**, which always gave material with a low allyl content, can be understood if structures such as **157** are present.

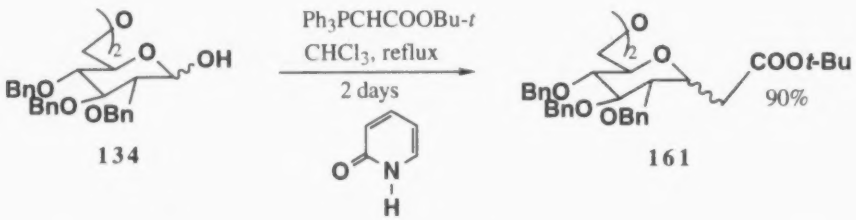
The other available disaccharide, which we had made by an unambiguous route (**134**), was now subjected to the reaction conditions that led to chain extension of the monosaccharide. The reaction produced a variety of products, which are not fully charaterized, as shown in Scheme 95. If



Scheme 95

heating was continued for longer periods and/or at higher

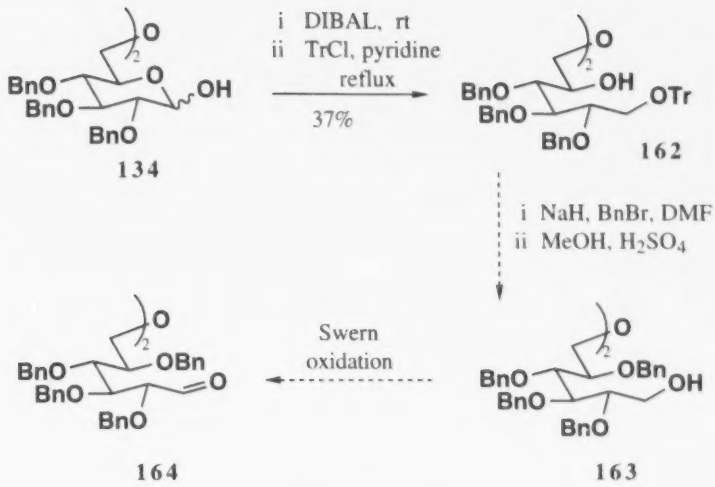
temperatures it was found that a large portion of the desired product underwent intramolecular Michael addition to afford compound **159**. In an effort to suppress this Michael addition other solvents were tried. Surprisingly, it was found that the use of chloroform led to a high yield (92%) of compound **160**, the mono olefination product, and a low yield (2%) of the bis addition product **158**. In an effort to improve the yield, the reaction mixture was refluxed but no improvement was observed. It is known that 2-pyridone catalyses mutarotation of sugars[113] and this compound was added to the reaction mixture (Scheme 96). This additive was found to increase the rate, but only the bis (chain extended) Michael product **161** was isolated.



134 161

Scheme 96

We decided to try to carry out a reduction, protection, deprotection, and oxidation sequence (Scheme 97) to solve



Scheme 97

the Michael addition problem.

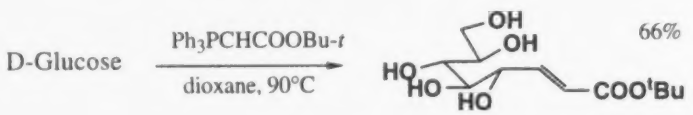
The reduction was originally tried with $NaBH_4$ but the resulting borate ester could not be hydrolyzed. The reduction was accomplished with several equivalents (5) of DIBAL, but reaction was very slow (24-30 h), probably because the anomeric hydroxyl was bound to the aluminum, making the aldehyde not very accessible. The product could not be readily purified, and so the primary hydroxyls were protected by tritylation to give compound **162** (37%). Benzylation of the free secondary hydroxyls appeared to go well (^1H NMR spectra) but the compound decomposed upon treatment with acidic methanol (for removal of the trityl protecting group). This route was abandoned because of the low yields.

V.8. Wadsworth-Horner-Emmons Chain Extension of Unprotected Carbohydrates

The ability to produce non-cyclized chain extended

carbohydrates using the Wadsworth-Horner-Emmons reaction would be useful, particularly if the substrates are not protected. There are very few examples of open chain higher sugars being produced via a Wadsworth-Horner-Emmons olefination[114] and the extent to which a Michael reaction occurs (see below) during the olefination depends not only on the reaction conditions,[112] but also on the nature of the substrate. The ability to carry out the reaction on unprotected sugars would have an added benefit because it lowers the number protection steps needed in a synthetic sequence. Thus, we wanted to explore the scope and utility of the chain extension method that we had discovered for unprotected carbohydrates.

We attempted the reaction illustrated in Scheme 98 on a variety of sugars and have come across none that are



152

Scheme 98

unreactive. In some cases reaction was slow, most notably 2-*N*-acyl-D-glucosamine, and the slower reaction rates were attributed to a lack of solubility of the carbohydrate in 1,4-dioxane. The results of these exploratory reactions are shown in Table 2. DMF was added to improve the solubility of the carbohydrate substrate, and it was found that the

reaction rates increased. Curiously, when reactions were

Table 2: Wittig Olefination of Selected Carbohydrates by Reaction with [Carbo(*t*-butyloxy)-methylene]triphenylphosphorane

SUGAR	YIELD (%) AND ISOMER RATIO (E:Z)[a]	COUPLING CONSTANTS $^3J_{H-2,H-3}$ (Hz)	PRODUCT COMPOUND #
D-Glucose	66 (*E* only)	17	**152**
D-Mannose	85 (2:1)	17 (*E*) and 12 (*Z*)	**165**
D-Galactose	76 (*E* only)	17	**166**
N-Acyl-D-glucosamine	48[b] (*E* only)	17	**167**
D-Ribose	58 (19:1)	17 (*E*) and 11 (*Z*)	**168**
D-Arabinose	92 (*E* only)	16	**169**

a - In all cases a second crystallization was carried out to separate isomers or effect further purification. The material from this crystallization was pure, except for the case of galactose, where <5 mole % of water was still present after vacuum drying.

b - corrected for recovered starting material

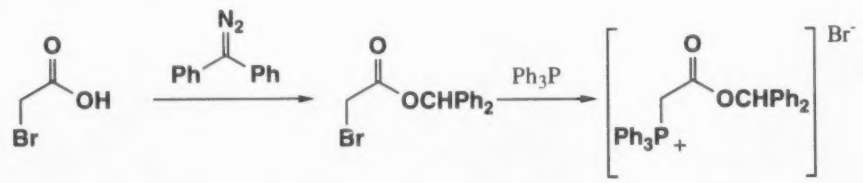
---

tried in DMF alone, very little, if any, olefination was observed. Hence, there appears to be a requirement for dioxane. The addition of DMF does, however, make crystallization of the chain-extended sugar more difficult.

The only product from the reaction appears to be the open chain form of the sugar. We found no evidence for

intramolecular Michael addition of hydroxyl groups of the α,β-unsaturated ester when the alkoxy portion of the ester is large and bulky. The *E* isomers all have olefinic coupling constants of 16 to 17 Hz and the geometry of the double bond was assigned based on these large $^{3}J_{H\text{-}2\text{-}H\text{-}3}$ values. In the cases where *Z* isomers were produced, the olefinic coupling constants were 10 to 12 Hz. (Occasionally, trace amounts of *Z* isomers were observed in the ^{1}H NMR spectra of products before crystallization.)

Conditions for removal of an *O*-*t*-butyl protecting group are quite vigorous (10-20% TFA in CH_2Cl_2) and are incompatible with many situations found in carbohydrate chemistry. For this reason, we wanted to prepare another reagent that could be deprotected by hydrogenation. A second advantage of such a reagent is that the olefin can be saturated and the protecting group removed in the same step. We decided to try to prepare [carbo(diphenylmethoxy)methylene]triphenylphosphorane. This meant that it was necessary to make the corresponding phosphonium salt **170**, as shown in Scheme 99.

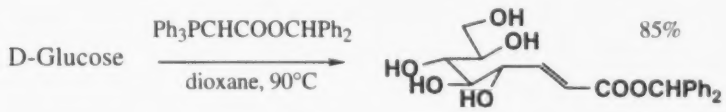


170

Scheme 99

First, the ester was prepared from 2-bromoacetic acid, using diphenyldiazomethane, and then treatment with triphenylphosphine gave the required salt **170**.

The homologation was tried using the above conditions, as illustrated in Scheme 100, with three sugars, and the



171

Scheme 100

results are summarized in Table 3. The product of all the

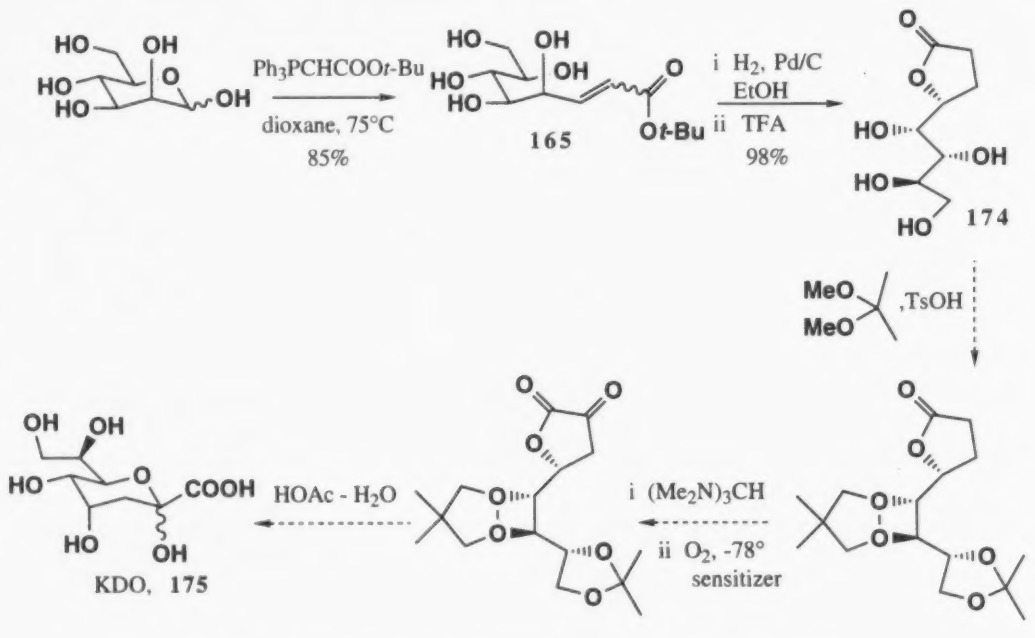
Table 3: Wittig Olefination of Selected Carbohydrates by Reaction with [Carbo(diphenylmethoxy)-methylene]triphenylphosphorane

SUGAR	YIELD (%) AND ISOMER RATIO (E:Z)	COUPLING CONSTANTS $^3J_{H-2,H-3}$ (Hz)	PRODUCT COMPOUND #
D-Glucose	85 (*E* only)	17	**171**
D-Galactose	60 (*E* only)	17	**172**
D-Mannose	73 (*E*), trace (*Z*)	17	**173**

reactions appears to be only the open chain form. Use of the new reagent also appears to have increased the selectivity for the *E* isomer. In the case of D-mannose, a trace of the *Z*

isomer is visible in the ^1H NMR spectrum of the product. The geometry of the olefinic bond was established on the basis of large values of the coupling constant between H-2 and H-3 (^3J = 17 Hz). Again, no evidence for Michael addition to the olefin by the C-4 hydroxyl group was found.

In order to demonstrate the synthetic utility of the new reaction it was decided to use it in a natural product synthesis. The target compound chosen was KDO (3-deoxy-**D**-*manno*-octulosonic acid) (**175**), which is one of the carbohydrates commonly found on the surfaces of bacterial



Scheme 101

cells, and which plays an important role in molecular recognition.[115] It was previously demonstrated[116] that

compound **174** could be converted to KDO (**175**) in three steps, as summarized in Scheme 101. The present route to **174** is shorter and gives a better yield than that used[116] earlier (83% *versus* 46%, from D-mannose).

V.9. Conclusions

1) A new methodology for two-carbon chain extension of unprotected monosaccharides has been developed and applied to D-glucose, D-galactose, D-mannose, D-*N*-acyl-glucosamine, D-ribose and D-arabinose. Two reagents for the chain extension have been developed and give similar results. The utility of the method was demonstrated by using it to prepare compound **174**. This preparation constitutes a formal synthesis of the natural product KDO (3-deoxy-**D**-*manno*-octulosonic acid) **175**.[116]

2) A procedure for coupling of monosaccharides to unambiguously give 6',6-anhydro disaccharides has been developed.

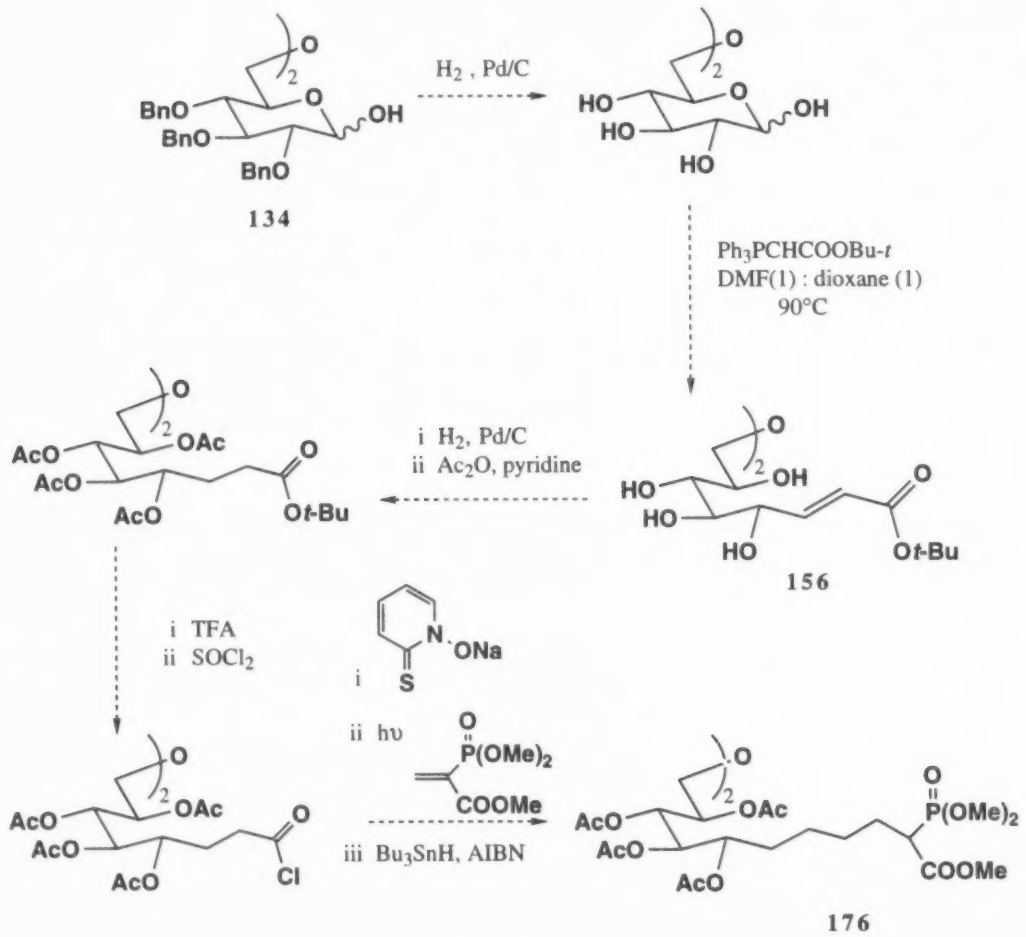
3) In the case of monosaccharides, a chain extension procedure was developed that leads to material with phosphonate and ester groups at the chain terminus. This procedure is based on radical decarboxylation and radical Michael addition. The $(MeO)_2P(O)$ and methyl ester groups that are introduced are an essential functionality for eventual coupling of this type of compound with polyene bis aldehyde **79**.

4) Polyethers can be prepared in a controlled manner

avoiding complex purification procedures needed in random synthetic approaches previously used.

5) The anion derived from triethyl phosphonoacetate is a poor nucleophile and its use in this capacity should be avoided.

6) Disaccharide **146**, reported by Whistler and Frowein,[85] is probably a mixture of D-glucose, **146**, and (mainly) higher order oligosaccharides (**157**) derived from **146**.



Scheme 102

7) It appears that approaches to the desired bis phosphonates **176** should start from compound **134**, as shown in Scheme 102. Debenzylation and Wittig olefination (Scheme 102) should lead to **156**, which could then be chain-extended, using the radical methodology already applied to monosaccharides, to give the precursor for macrocyclization **176**.

VI. Experimental

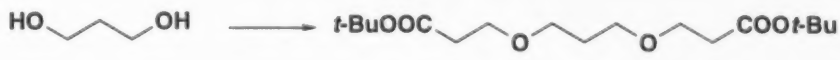
General:

In addition to the general remarks in Part I, Chapter III, the following particulars apply: Optical rotations were measured using a Perkin-Elmer 241 Polarimeter with a 10 cm path length at 25 °C. In some experiments the symbols s', d', t' and q' have been used for ^{13}C NMR signals in APT (attached proton technique) spectra and indicate 0, 1, 2, or 3 attached hydrogens.

The following is a list of compounds that were prepared using the procedures already described in the literature: 1,2:5,6-*O*-diisopropylidene-α-**D**-*gluco*furanose (**74**),[117] 1,2-*O*-isopropylidene-α-**D**-*gluco*furanose (**75**),[121] 5,6-anhydro-1,2-*O*-isopropylidene-α-**D**-*gluco*furanose (**76**),[118] D-glucose diethyl dithioacetal (**114**),[119] 6-*O*-benzoyl-**D**-glucose diethyl dithioacetal (**115**),[98] 6-*O*-benzoyl-2,3:4,5-di-*O*-isopropylidene-**D**-glucose diethyl dithioacetal (**116**),[98] α- and β-2,3:4,5-di-*O*-isopropylidene-**D**-*gluco*septanose (**117**),[98] 1,2:5,6-*O*-diisopropylidene-α-**D**-*galacto*pyranose (**123**),[120] 1,2:3,4-di-*O*-isopropylidene-α-**D**-*galacto*-1,6-hexadialdo-1,5-pyranose (**124**),[106] methyl 6-*O*-trityl-α-**D**-*gluco*pyranoside (**127**),[109] methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-**D**-*gluco*pyranoside (**128**),[109] methyl 2,3,4-tri-*O*-benzyl-α-**D**-

*gluco*pyranoside (**129**),[109] 1,2-*O*-isopropylidene-6-*O*-toluenesulfonyl-α-**D**-*gluco*furanose (**145**),[85] (*E*)-6,7-dideoxy-7-phenyl-**L**-heptenitol (**148**),[89] 1,1-dimethylethyl 2-(triphenylphosphonium)acetate bromide.[122]

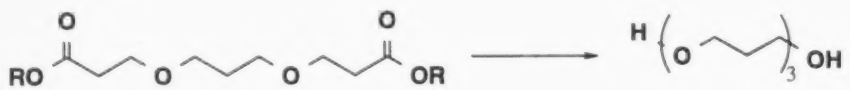
4,8-Dioxaundecan-1,11-dioic acid, bis(1,1-dimethylethyl) ester (82).



$Hg(OAc)_2$ (9.63 g, 29.4 mmol) was added to ethanediol (1.00 mL, 1.05 g, 13.8 mmol). *t*-Butyl acrylate (10.00 mL, 8.75 g, 68.6 mmol) was then added and the mixture was subjected to ultrasound for one week (Branson Model B12), the ultrasound bath being cooled by passing a slow stream of water through a copper tube immersed in the bath. The *t*-butyl acrylate was then evaporated and the residual solid was dissolved in MeOH (25 mL) and cooled (-78 °C). $NaBH_4$ (2.18 g, 57.7 mmol) was then added slowly (caution: exothermic reaction) with stirring. After 3 h, glacial AcOH (10 mL) was added, and the mixture was filtered through Celite. The filter cake was washed with EtOAc (2 x 100 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (300 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 40% EtOAc-hexane, gave **82** (3.08 g, 67%) as an oil: FT-IR ($CHCl_3$ cast) 1731, 1161, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz)

δ 1.43 (s, 18 H), 1.78 (ap qt, *J* = 6 Hz, 2 H), 2.44 (ap t, *J* = 7 Hz, 4 H), 3.48 (t, *J* = 6 Hz, 4 H), 3.63 (ap t, *J* = 7 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.99, 29.99, 36.34, 68.44, 67.85, 80.41, 170.94; exact mass *m/z* calcd for $C_{17}H_{33}O_6$ (M + H) 333.2277, found 333.2264. Anal Calcd for $C_{17}H_{32}O_6$: C, 61.42; H, 9.70. Found: C, 61.77; H, 9.77.

4,8-Dioxaundeca-1,11-diol (83).



Method A (preparation from dimethyl ester **81**):

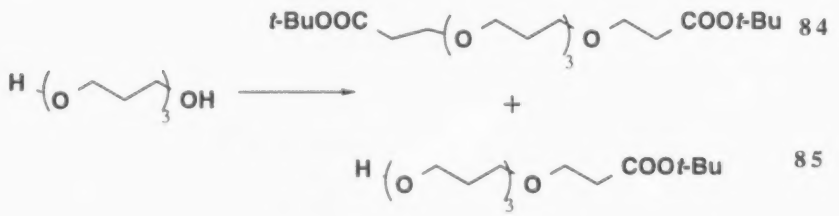
A solution of the dimethyl ester **81** (3.0 g, 12 mmol) in dry THF (20 mL plus 5 mL as a rinse) was added via cannula, using a positive pressure of Ar, to a stirred suspension of $LiAlH_4$ (95%, 2.14 g, 53.6 mmol) and THF (100 mL). The mixture was refluxed for 2 h, opened to the air and cooled to room temperature. EtOAc (20 mL) was added (stirring) and the mixture was stirred overnight, acidified with concentrated hydrochloric acid (*ca.* 3 mL) and filtered through Celite. The Celite pad was washed with MeOH (3 x 125 mL). The filtrate was evaporated and the residue was then dissolved in CH_2Cl_2 (*ca.* 200 mL), and dried ($MgSO_4$). The drying agent and flask were washed with CH_2Cl_2 (3 x 100 mL), and the combined filtrates and washings were evaporated. Flash chromatography of the residue over silica gel (7 x 25 cm), using 5% MeOH-

EtOAc, gave **83**, as an oil [1.26 g, 77% corrected for recovered starting material (2.75 g)]: R_f = 0.21; FT-IR (neat film) 3600-3200, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ = 1.78 (m, 6 H), 3.15 (br s, 2 H), 3.49 (ap t, J = 6 Hz, 4 H), 3.57 (ap t, J = 6 Hz, 4 H), 3.72 (ap t, J = 6 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 29.84, 31.94, 61.26, 68.04, 69.58; mass (CI) *m/z* calcd for $C_9H_{20}O_4$ 192, found 193 (M + 1).
NOTE: The TLC plates are best visualized using a vanillin dip which is prepared by dissolving vanillin (*ca.* 15 g) in 95% EtOH (50 mL) and then adding concentrated H_2SO_4 (5 mL) with cooling. The plates are warmed using a heat gun (best) or hot plate.

Method B (from di-*t*-butyl ester **82**):

A solution of di-*t*-butyl ester **82** (2.02 g, 6.09 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (95%, 1.32 g, 33.1 mmol) in THF (125 mL). The mixture was refluxed for 5 days and then cooled to room temperature. EtOAc (15 mL) was added and the mixture was stirred for 1 h. The mixture was acidified with concentrated hydrochloric acid (pH paper), and solid $NaHCO_3$ was added to neutrality (pH paper). The mixture was dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5.5 x 25 cm), using 5% MeOH-EtOAc, gave **83** (0.841 g, 72%) as a viscous oil (R_f = 0.20) whose spectral data were identical to those for material made from the methyl ester.

4,8,12,16-Tetraoxanonadecan-1,19-dioic acid, bis(1,1-dimethylethyl) ester (84) and 15-hydroxy-4,8,12-trioxapentadecan-1-oic acid, 1,1-dimethylethyl ester (85).



A mixture of the trimeric diol **83** (0.606 g, 3.16 mmol), $Hg(OAc)_2$ (2.53 g, 7.94 mmol), and *t*-butyl acrylate (added in this order) was subjected to ultrasound for one week (Branson Model B12), the sonicating bath being cooled by a copper coil carrying a slow stream of water. The acrylate was evaporated and the residue was then dissolved in MeOH (50 mL). The solution was cooled (-78 °C). $NaBH_4$ (1.18 g, 31.2 mmol) was cautiously added and the mixture was stirred for 1 h. Glacial AcOH (*ca.* 6 mL) was added, and the mixture was filtered through Celite. The filter pad was washed with EtOAc (3 x 75 mL). The combined washings were placed in a separatory funnel, and washed with brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 40% EtOAc-hexane, gave **84** (17.6 mg, 1.6%) as an oil: R_f = 0.48; FT-IR ($CHCl_3$ cast) 1731, 1159, 1113 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 18 H), 1.60-1,72 (m, 6 H), 2.34 (ap t, J = 7 Hz, 4 H), 3.33 (m,

12 H), 3.52 (ap t, J = 7 Hz, 4 H); ^{13}C NMR ($CDCl_3$. 75 MHz) δ 28.17, 29.75, 30.10, 30.18, 66.55, 67.85, 67,94, 68.05, 80.48, 171.01; mass (CI) m/z calcd for $C_{23}H_{44}O_8$ 448, found 466 (M + 18). The mono addition product **85** (160 mg, 16%) was isolated as an oil: R_f = 0.08; FT-IR ($CHCl_3$ cast) 3600-3200, 1731, 1161, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9 H), 1.76-1.87 (m, 6 H), 2.45 [overlapping ap t and s, J = 7 Hz, 3 H, (CH_2 and OH)], 3.41-3.53 (m, 8 H), 3.59 (ap t, J = 7 Hz, 2 H), 3.64 (ap t, J = 7 Hz, 2 H), 3.73 (ap t, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.12, 29.99, 30.07, 30.65, 36.40, 62.01, 66.49, 67.76, 67.83, 67.95, 68.34, 70.16, 80.48, 171.04; mass (CI) m/z calcd for $C_{16}H_{32}O_6$ 320, found 321 (M + 1).

4,8,12,16-Tetraoxanonadecan-1,19-diol (86).

Diol **83** (0.562 g, 2.93 mmol) was dissolved in acrolein (25.0 mL, 22.3 g, 396 mmol), and $Hg(OAc)_2$ (4.27 g, 13.40 mmol) was added, producing a yellow-grey solution, which was stirred for 2 days. The excess of acrolein was evaporated and the residue was dissolved in MeOH (30 mL) and CH_2Cl_2 (5 mL). The solution was cooled (-78 °C) and $NaBH_4$ (1.10 g, 29.1 mmol) was added very cautiously. After 1 h the cooling bath was removed and the mixture was allowed to warm to room

temperature. It was then acidified with 2 N hydrochloric acid (pH paper) and then solid $NaHCO_3$ was added to neutrality (pH paper). The mixture was filtered through Celite (3 x 5 cm), and the pad was washed with EtOAc (2 x 25 mL). The filtrate was evaporated and the residue was dissolved in CH_2Cl_2, dried ($MgSO_4$), and filtered through flash chromatography silica gel (3 x 5 cm). The silica was washed sequentially with EtOAc (500 mL), acetone (500 mL), and MeOH (250 mL). The desired product was mainly in the acetone fraction, which was evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% acetone-EtOAc, gave **86** (0.835 g, 60% corrected for polymeric impurity based on ^1H NMR (200 MHz) estimate) as an impure oil: R_f = 0.24; FT-IR ($CHCl_3$ cast) 3600-3100, 1111, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ = 1.60-1.91 (m, 12 H), 3.55 (ap t, J = 6 Hz, 8 H), 3.63 (ap t, J = 6 Hz, 8 H), 3.75 (ap t, J = 6 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 29.85, 31.87 (two coincident signals), 61.45, 68.16 (two coincident signals), 69.75 (two coincident signals); mass (FAB) *m/z* calcd for $C_{15}H_{32}O_6$ 308, found 308. The material was contaminated with *ca.* 5 mol% (^1H NMR, 200 MHz) of a polymeric material derived from acrolein.

A bis benzoyl ester derivative was prepared as follows: Pyridine (0.30 mL, 0.29 g, 3.7 mmol) and benzoyl chloride (0.25 mL, 0.30 g, 2.2 mmol) were added to a stirred and cooled (-78 °C) solution of **86** (62.8 mg, 0.20 mmol) in CH_2Cl_2 (10 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. The solution was

poured into 2 N hydrochloric acid (50 mL), and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using first 40% EtOAc-hexane (*ca.* 500 mL) and then 80% EtOAc-hexane, gave the bis benzoyl derivative (76.4 mg, 73%): FT-IR ($CHCl_3$ cast) 1716, 1601, 1584, 1178, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.73-1.93 (m, 6 H), 2.04 (ap qt, J = 6 Hz, 4 H), 3.42-3.62 (m, 16 H), 4.42 (ap t, J = 6 Hz, 4 H), 7.38-7.62 (m, 6 H), 8.01-8.10 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.14, 29.70, 30.07, 62.31, 67.41 (2 coincident peaks), 67.95 (2 coincident peaks), 128.39, 129.60, 129.67, 132.91, 182.31; mass (CI) *m/z* calcd for $C_{29}H_{40}O_8$ 516, found 517 (M + 1).

Compounds **71** and **88** to **99** were previously reported in reference 81. However, no experimental details or spectral data were given and thus the experiments have been included here.

Tropylium tetrafluoroborate (88).

This compound is commercially available from Aldrich Chemical Company; however, it was prepared using the

following procedure. Aqueous HBF_4 (48% w/v, 70 mL) was added cautiously, to cooled (0 °C) and stirred acetic anhydride (300 mL). (The addition of HBF_4 to Ac_2O, which is carried out in a beaker, is very exothermic.) After the addition, the ice bath was removed, and Ph_3COH (100 g, 0.384 mol) was tipped in. The resulting orange-yellow solution was poured into anhydrous Et_2O, producing a yellow precipitate which was filtered off and washed with dry Et_2O (3 x 100 mL).[123] The solid was then dissolved in dry CH_3NO_2 (500 mL) by slowly pouring the solvent through the filter cake. Cycloheptatriene (**87**) (31.00 mL, 24.78 g, 0.269 mol) was added with stirring to the orange-red nitromethane solution. Stirring was continued for 15 min, and the solution was then poured into dry Et_2O (1 L). The resulting white precipitate was washed with dry Et_2O until the washings were colorless, and then dried (oil pump vacuum) to afford tropylium tetrafluoroborate **88** (46.3 g, 97%): decomposition at >210 °C; FT-IR (nujol mull) 3030, 1479, 1377 cm^{-1}; exact mass *m/z* calcd for C_7H_7 91.0548, found 91.0584. Anal Calcd for $C_7H_7BF_4$: C, 47.25; H, 3.97. Found: C, 47.03; H, 3.90.

3,5-Cycloheptadien-1-ol (90).[81]

Tropylium tetrafluoroborate **88** (41.99 g, 236 mmol) was dissolved in bench CH_3NO_2 (500 mL). Na_2CO_3 (31.00 g, 292 mmol) was added, and the mixture was refluxed for 30 min, cooled to room temperature, filtered, and evaporated. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with water (200 mL) and brine (200 mL), and evaporated.[93,94] The residue was dissolved in a mixture of MeOH (467 mL) and water (33 mL) and cooled in an ice bath. $NaBH_4$ (15.00 g, 397 mmol) was added with stirring and at a rate that kept the temperature below 10 °C. The cold bath was left in place and stirring was continued overnight. The pH was adjusted to 6 (pH paper) by addition of glacial AcOH (20 mL), and then saturated aqueous $NaHCO_3$ was added until the pH reached 7. The neutral solution was poured into saturated aqueous $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (4 x 150 mL). The organic extract was washed with brine (200 mL), dried ($MgSO_4$), and evaporated. Short path vacuum distillation (bp 66 °C, 0.70 Torr) of the residue gave **90** as a colorless oil (7.34 g, 28%): FT-IR ($CHCl_3$ cast) 3600-3200, 1055, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.22 (br s, 1 H), 2.42-2.60 (m, 4 H), 4.18 (tt, J = 5, 5 Hz, 1 H), 5.58-5.71 (m, 2 H), 5.71-5.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.39, 68.56, 120.06, 126.28; exact mass m/z calcd for $C_7H_{10}O$ 110.0732, found 110.0728.

3,5-Cycloheptadien-1-yl-[(1,1-dimethyl)dimethylsilyl] ether (91).[81]

TBDMSCl (9.40 g, 62.4 mmol) and then imidazole (4.50 g, 66.2 mmol) were added to a stirred solution of compound **90** (6.25 g, 56.8 mmol) in CH_2Cl_2 (250 mL). The mixture was stirred at room temperature for 20 h and the imidazolium salt was filtered off. The filtrate was poured into water (100 mL), and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (11 x 20 cm), using 20% EtOAc-hexane, gave **91** (12.01 g, 94%) as a colorless oil: R_f = 0.80; FT-IR (neat film) 3021, 1522, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 6 H), 0.89 (s, 9 H), 2.42-2.58 (m, 4 H), 4.00-4.14 (m, 1 H), 5.58-5.85 (br m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.72, 18.24, 25.93, 40.99, 71.50, 126.09, 128.12; exact mass *m/z* calcd for $C_{13}H_{24}OSi$ 224.1596, found 224.1594.

α,α,α-6,7-Dioxabicyclo[3.2.2]non-8-en-3-yl-[(1,1-dimethylethyl)dimethylysilyl] ether (92).[81]

meso-Tetraphenylporphine (*ca.* 15 mg) was added to a solution of compound **91** (8.10 g, 36.1 mmol) in 71.5:28.5 (v/v) CH_2Cl_2:MeOH (350 mL) contained in a pyrex vessel, and the resulting purple solution was cooled to -20 °C. Oxygen was bubbled through the solution, which was irradiated using a Na/Hg lamp (Philips High Pressure Ceramalux C400s51 Δ09-1 Hg/Na) for 11 h, during which time the temperature rose to *ca.* 0 °C. The solvent was then evaporated, and flash chromatography of the crystalline residue over silica gel (11 x 20 cm), using 5% EtOAc-hexane, gave three fractions. The desired bicyclic peroxide **92** (6.69 g, 72%, 60% after correction for the amount of undesired *exo* isomer) was isolated as a mixture of isomers [83:17 *endo*:*exo* (^{1}H NMR, 300 MHz)]. The product was a semicrystalline solid: mp room temperature to 68 °C; FT-IR (nujol mull) 3062, 1091, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 6 H), 0.87 (s, 9 H), 1.77-2.50 (m, 4 H), 3.62-3.81 (m, 1 H), 4.58-4.72 (m, 2 H), 6.36 (dd, *J* = 6, 4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.67, 18.04, 25.80, 41.05, 66.29, 73.50, 128.72; mass (CI) *m/z* calcd for $C_{13}H_{24}O_3Si$ 256, found 274 (M + 18). Anal Calcd for $C_{13}H_{24}O_3Si$: C, 60.89; H, 9.43. Found: C, 60.92; H, 9.48. An analytical sample of the *exo* isomer was isolated by chromatography (3% EtOAc-hexane, silica) and had: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.90-2.30 (m, 4 H), 3.61-3.73 (m, 1 H), 4.52-4.63 (m, 2 H), 6.40-6.49 (m, 2 H); mass (CI) *m/z* calcd for $C_{13}H_{24}O_3Si$ 256, found 274 (M + 18).

[[(1,1-Dimethylethyl)dimethylsilyl]oxy]cyclohept-6-en-1,5-diol (93).[81]

Zinc dust (14.85 g, 227 mmol) was added cautiously to a cooled (ice-water bath) and stirred solution of bicyclic peroxide **92** (8.31 g, 32.4 mmol, a 19:1 mixture of *exo* and *endo* isomers based on a ^1H NMR estimate) in CH_2Cl_2 (400 mL), and then glacial AcOH (38.00 mL, 39.52 g, 658 mmol) was added. The resulting mixture was stirred for 18 h, during which time the cooling bath attained room temperature. The mixture was filtered through a pad of coarse silica gel to remove the excess of zinc dust. The silica was washed with EtOAc (3 x 100 mL) and the filtrate was concentrated to *ca.* 300 mL. The solution was washed with saturated aqueous $NaHCO_3$ (250 mL), some solid $NaHCO_3$ being added to the separatory funnel until gas evolution stopped. The organic phase was separated, washed with brine (200 mL), dried ($MgSO_4$), and evaporated, the last traces of solvent being removed under oil pump vacuum (12 h). The desired diol **93** (7.95 g, 95%) was obtained as a mixture of *syn* (19) and *anti* (1) isomers, the ratio being the same as in the starting material, in the form of a waxy solid that was a mixture of plates and needles: mp 99-101 °C; FT-IR ($CHCl_3$ cast) 3600-

3200, 1522, 1125, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 6 H), 0.87 (s, 9 H), 1.8-2.13 (br m, 6 H), 3.95-4.08 (m, 1 H), 4.20-4.35 (m, 2 H), 5.72 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.68, 18.02, 25.79, 45.05, 67.28, 69.08, 134.77; mass (CI) *m/z* calcd for $C_{13}H_{26}O_3Si$ 258, found 259 (M + 1). Anal Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.75; H, 10.30.

***Meso*-1,5-Bis(benzyloxy)-3-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]cyclohept-6-ene (94).**[81]

Compound **93** (5.10 g, 19.8 mmol, *syn* (19) to *anti* (1) molar ratio based on ^1H NMR estimate) was dissolved in dry THF (75 mL) and benzyl bromide (26.00 mL, 37.8 g, 217 mmol) was added to the stirred solution. Then 60% NaH (4.95 g, 123.8 mmol) was cautiously added (evolution of hydrogen). The reaction mixture was refluxed for 4 h, cooled to room temperature, and filtered through coarse silica gel (5 x 2 cm). The filtrate was washed with saturated aqueous NH_4Cl (250 mL) (NH_3 evolved, fume hood). The aqueous layer was back-extracted with CH_2Cl_2 (50 mL) and the organic extracts were combined and washed with saturated aqueous $NaHCO_3$ (200 mL), dried ($MgSO_4$), and evaporated. The benzyl bromide was

removed by simple vacuum distillation. The residual *anti* isomer (0.420 g) was removed during flash chromatography through silica gel (6 x 20 cm), using 10% Et_2O-hexane, which gave **94** (8.03 g, 97%, after correction for recovered *anti* isomer) as a yellow semisolid: R_f = 0.23; mp 21-25 °C (no literature value was given); FT-IR (film) 3600-3200, 3125, 3117, 1492, 1113, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.11 (s, 6 H), 0.90 (s, 9 H), 1.64 (q, *J* = 12 Hz, 2 H), 2.14 (br d, *J* = 12 Hz, 2 H), 3.79 (tt, *J* = 12, 4 Hz, 1 H), 3.90 (br d, *J* = 11 Hz, 2 H), 4.53 (d, *J* = 12 Hz, 2 H), 4.64 (d, *J* = 12 Hz, 2 H), 5.91 (s, 2 H), 7.30-7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.65, 18.10, 25.84, 42.63, 69.96, 70.60, 73.52, 127.57, 127.64, 128.46, 134.09, 138.40; mass (CI) *m/z* calcd for $C_{27}H_{38}O_3Si$ 438, found 438. Anal Calcd for $C_{27}H_{38}O_3Si$: C, 72.93; H, 8.74. Found: C, 72.92; H, 8.92.

***Meso*-2,6-Bis(benzyloxy)-4-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]hepta-1,7-diol (95).**[81]

Protected triol **94** (7.07 g, 16.1 mmol) was dissolved in 1:1 (v/v) MeOH:CH_2Cl_2 (350 mL) and cooled (dry ice/acetone bath). Ozone was bubbled through the solution until a blue

color persisted. The mixture was stirred and $NaBH_4$ (3.86 g, 102 mmol) was added. The cold bath was left in place and stirring was continued overnight. Glacial AcOH was added until an acidic solution resulted (pH paper), followed by saturated aqueous $NaHCO_3$, until pH 7 was reached. The mixture was poured into a separatory funnel and extracted with CH_2Cl_2 (3 x 200 mL). The organic phase was separated and washed with brine (200 mL). The aqueous layer was further extracted with CH_2Cl_2 (100 mL), and the organic extracts were combined, dried ($MgSO_4$), evaporated, and then placed under high vacuum. The oily product **95** (7.51 g, 98%) was not further purified: FT-IR ($CHCl_3$ cast) 3600-3200, 1494, 1109, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.63-1.98 (m, 4 H), 2.32 (br s, 2 H), 3.44-3.78 (m, 6 H), 3.98 (tt, J = 6, 6 Hz, 1 H), 4.57 (ap s, 4 H), 7.37 (s, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.52, 17.96, 25.84, 38.45, 64.15, 66.99, 71.36, 76.39, 127.81 (shoulder present), 128.51, 138.30; mass (CI) *m/z* calcd for $C_{27}H_{42}O_5Si$ 474, found 492 (M + 18). Anal Calcd for $C_{27}H_{42}O_5Si$: C, 68.31; H, 8.92. Found: C, 68.33; H, 8.99.

***Meso*-2,6-Bis(benzyloxy)-4-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-1,7-bis(methanesulfonyloxy)heptane (96).**[81]

Triethylamine (18.0 mL, 13.1 g, 130 mmol) was added to a stirred and cooled (ice-bath) solution of diol **95** (3.01 g, 6.35 mmol) in CH_2Cl_2 (40 mL). Freshly distilled $MeSO_2Cl$ (4.00 mL, 5.83 g, 51.1 mmol) was added cautiously (exothermic reaction). The resulting yellow mixture, which gradually turned brown, was stirred for 3 h, poured into a mixture of ice (50 mL) and 2 N hydrochloric acid (50 mL), and extracted with CH_2Cl_2 (3 x 100 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (150 mL), and brine (150 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 40% EtOAc-hexane, gave **96** (3.45 g, 86%) as an oil: R_f = 0.33; FT-IR ($CHCl_3$ cast) 3088, 3062, 3025, 1176, 1118 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 6 H), 0.85 (s, 9 H), 1.51-1.82 (m, 4 H), 2.92 (s, 6 H), 3.68-3.78 (m, 2 H), 3.91 (tt, J = 6, 6 Hz, 1 H), 4.02 (dd, J = 5, 5 Hz, 2 H), 4.27 (dd, J = 11, 5 Hz, 2 H), 4.47 (d, J = 11 Hz, 2 H), 4.54 (d, J = 11 Hz, 2 H), 7.33 (s, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.52, 17.91, 25.82, 37.54, 38.01, 65.99,

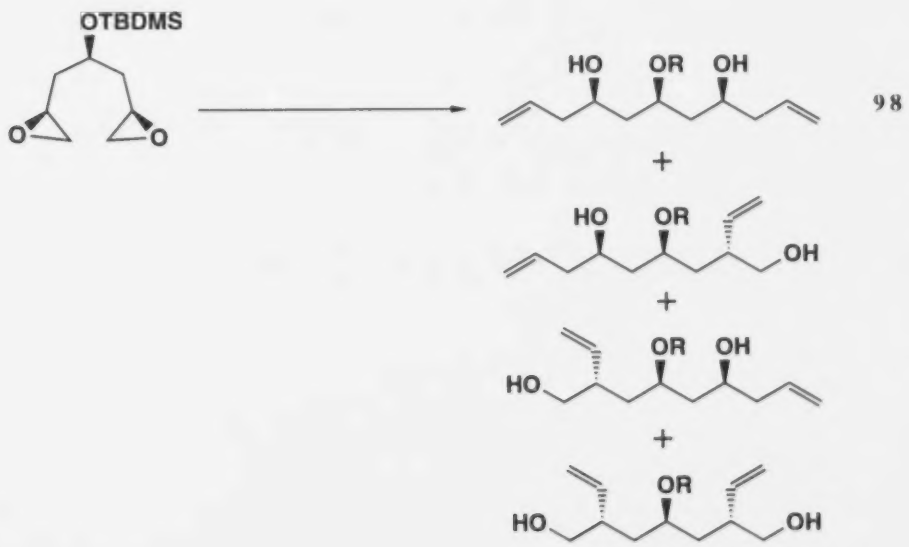
70.93, 71.91, 73.66, 127.88 (two coincident peaks), 128.47, 137.75; mass (CI) *m/z* calcd for $C_{29}H_{46}O_9S_2Si$ 630, found 648 (M + 18). Anal Calcd for $C_{29}H_{46}O_9S_2Si$: C, 55.21; H, 7.35. Found: C, 55.21; H, 7.43.

***Meso*-1,2:6,7-Dianhydro-3,5-dideoxy-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]*xylo*-heptitol (97).[81]**

Compound **96** (1.68 g, 2.66 mmol) was dissolved in 95% EtOH (25 mL), and glacial AcOH (4.5 mL), and $Pd(OH)_2/C$ catalyst (1 g) were added.[96] The mixture was placed in a Parr shaker under 65 psi of H_2. After 4 h more catalyst (1 g) was added and the reaction was continued for *ca.* 20 h (TLC control, silica, 10% EtOAc-hexane). The catalyst was filtered off and washed with EtOAc (10 x 50 mL), and the filtrate was poured into aqueous $NaHCO_3$ (200 mL). The layers were separated, and the organic phase was washed with brine (200 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH (1 L) and K_2CO_3 (2.13 g, 15.4 mmol) was added. The mixture was stirred at room temperature for 2 h, the bulk of the MeOH was evaporated (to approx. 100 mL) and the mixture was poured into brine (200 mL) and extracted with

CH_2Cl_2 (3 x 100 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexane, gave **97** (0.46 g, 67%) as an oil: R_f = 0.49 (silica, 20% EtOAc-hexane); FT-IR ($CHCl_3$ cast) 1100, 1081, 1060, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 6 H), 0.87 (s, 9 H), 1.68-1.93 (m, 4 H), 2.47 (dd, J = 6, 4 Hz, 2 H), 2.75 (dd, J = 5, 4 Hz, 2 H), 2.97-3.11 (m, 2 H), 4.09 (tt, J = 6, 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.66, 18.02, 25.79, 39.95, 46.75, 49.23, 68.49; mass (CI) m/z calcd for $C_{13}H_{26}O_3Si$ 258, found 259 (M + 1). The compound is volatile and should not be placed under high vacuum.

***Meso*-6-[[(1,1-Dimethyl)dimethylsilyl]oxy]undec-1,10-dien-4,8-diol (98).**[81]



98

Vinyl magnesium bromide (13.00 mL, 1 M in THF, 13.00 mmol) was added to CuCN (1.20 g, 13.4 mmol) contained in a dry three-necked flask cooled by a dry ice/acetone bath. Dry THF (10 mL) was added to aid stirring and the mixture was stirred for 30 min at -78 °C. A solution of bis epoxide **97** (1.49 g, 5.76 mmol) in dry THF (13.0 mL) was slowly added over 10 min from a dropping funnel. The dropping funnel was then rinsed with dry THF (7.0 mL). The cold bath was replaced with another cold bath charged with CCl_4 and dry ice, so as to maintain the reaction mixture at -15 °C to -20 °C. After 4.5 h a 9:1 solution of ammonium hydroxide in saturated aqueous NH_4Cl (10.0 mL) was added. The resulting mixture was warmed to room temperature, and filtered through a pad (5 x 2 cm) of Celite to remove solid particles.[124] The Celite was washed with EtOAc (3 x 75 mL) and the combined filtrates were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 20% EtOAc-hexane, gave **98** (1.62 g, 89%) as an oil. The desired diol **98** made up *ca.* 80% of this material (^1H NMR, 200 MHz estimate).[a] The isomer mixture had: FT-IR (CH_2Cl_2 cast) 3500-3200, 1642, 1075, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) [only peaks attributed to compound **98** are given] δ 0.12 (s, 6 H), 0.88 (s, 9 H), 1.50-1.81 (m, 4 H), 2.10-2.33 (m, 4 H), 2.56 (br s, 2 H), 3.73-3.88 (m, 2 H), 4.18 (tt, *J* = 8, 8 Hz, 1 H), 5.05-

[a] Peaks at δ 3.33-3.56 (minor components, integration = 4) vs. 3.70-3.84 (major components, integration = 21) were used to estimate purity. 21/(4+21)x100%=84% desired isomer.

5.19 (m, 4 H), 5.69-5.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) [mixture of isomers, peaks due to minor isomers marked with *] δ -4.34*, -4.29, 15.67*, 17.87, 25.85, 42.54*, 43.35, 43.46*, 43.51*, 43.60, 68.6*, 68.83*, 68.90, 69.04*, 69.57*, 70.22*, 70.95, 118.06, 118.28*, 134.45*, 134.61; mass (FAB) *m/z* calcd for $C_{17}H_{35}O_3Si$ (M + H) 315, found 315.

Meso-4,6,8-Tris[[(1,1-dimethylethyl)dimethylsilyl]-oxy]undeca-1,10-diene (99).[81]

mixture of isomers — mixture of isomers

R = TBDMS

TBDMSCl (2.48 g, 16.5 mmol) and then imidazole (1.80 g, 26.5 mmol) were added to a stirred solution of diol **98** (1.00 g, 3.20 mmol, a mixture of isomers containing *ca.* 80 mol% of the desired compound by ^1H NMR estimate) in CH_2Cl_2 (12.0 mL). The mixture was stirred at room temperature for 20 h, and then poured into saturated aqueous $NaHCO_3$ (250 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL), and the organic layer was washed with brine (200 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 5% EtOAc-hexane, gave **99** (1.52 g, 88 %) as a colorless oil, which was still a mixture of isomers: R_f = 0.57; FT-IR ($CDCl_3$ cast) 3086, 1120-1030 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) (only peaks attributed to compound **99** given) δ 0.05-0.12 (3 x s, 18 H), 0.87-0.98 (ap s, 27 H), 1.55-1.71 (m, 4 H), 2.18-2.41 (m, 4 H), 3.70-3.91 (m, 3 H), 5.01-5.15 (m, 4 H), 5.70-5.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) [mixture of isomers, signals of minor components marked with *] δ -4.30*, -4.25, -4.18, -4.12, 17.70*, 18.04, 18.14, 25.80*, 25.90*, 26.01 (two coincident peaks), 38.37*, 38.67*, 41.96, 42.12*, 43.74*, 43.95*, 45.23*, 45.61, 66.48*, 66.80*, 67.12, 69.03*, 69.23, 116.90, 117.15*, 134.97*, 135.29; mass (CI) *m/z* calcd for $C_{29}H_{62}O_3Si_3$ 542, found 543 (M + 1).

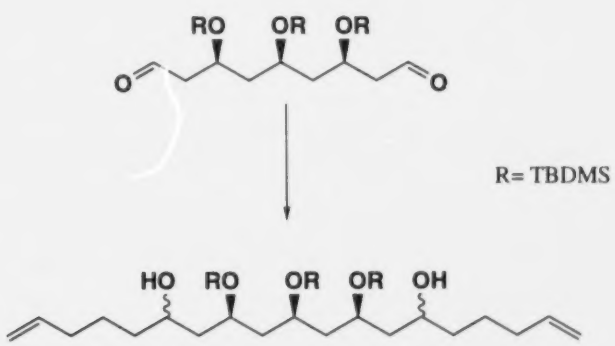
***Meso*-3,5,7-Tris[[(1,1-dimethylethyl)dimethylsilyl]-oxy]nonane-1,9-dial (71).**[81]

R = TBDMS

Ozone was bubbled through a cooled (dry ice-acetone) solution of fully protected triol **99** (2.01 g 3.71 mmol, mixture of isomers containing *ca.* 80% of desired isomer by ^{1}H NMR estimate) in 1:1 CH_2Cl_2:MeOH (50 mL) until a blue color persisted. Ar was bubbled through the solution to discharge the blue color and Ph_3P (2.21 g, 8.44 mmol) was then added. The cold bath was left in place, but not recharged, and the mixture was stirred overnight. The solution was poured into saturated aqueous $NaHCO_3$ (100 mL), and extracted with CH_2Cl_2

(3 x 50 mL). The extract was washed with brine (200 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using 5% EtOAc-hexane, gave **71** as an oil (1.51 g, 74%, 93% corrected for purity of starting material): R_f = 0.21; FT-IR ($CHCl_3$ cast) 1727, 1108, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 6 H), 0.06 (s, 6 H), 0.09 (s, 6 H), 0.87 (s, 18 H), 0.88 (s, 9 H), 1.62-1.85 (m, 4 H), 2.41-2.68 (m, 4 H), 3.82 (ap qt, *J* = 7 Hz, 1 H), 4.32 (ap qt, *J* = 6 Hz, 2 H), 9.80 (dd, *J* = 3, 2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.50, -4.26 (two coincident peaks), 17.95 (two coincident peaks), 25.79, 25.87, 45.56, 50.93, 65.44, 66.53, 201.62; mass (CI) *m/z* calcd for $C_{27}H_{58}O_5Si_3$ 546, found 547 (M + 1). Anal Calcd for $C_{27}H_{58}O_5Si_3$: C, 59.29; H, 10.69. Found: C, 59.55; H, 10.37.

Meso-8,10,12-Tris[[(1,1-dimethylethyl)dimethylsilyl]-oxy]nonadeca-1,18-dien-6,14-diol (100).

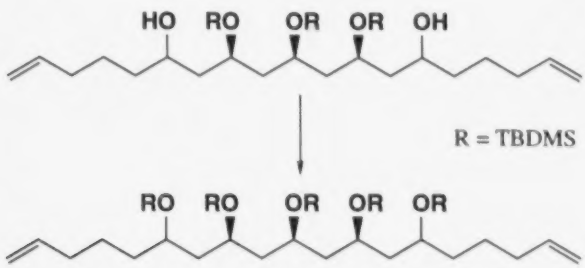


5-Bromopentene (1.40 mL, 1.76 g, 11.8 mmol) was added to a mixture of magnesium (0.486 g, 20.0 mmol) and dry THF (50

mL). The mixture was stirred briefly at room temperature, and then refluxed for 1 h. The resulting Grignard reagent was then cooled (ice bath) and a solution of bis aldehyde **71** (1.46 g, 2.67 mmol) in dry THF (5.00 mL) was added dropwise over 5 min from a dropping funnel. The funnel was washed with THF (3.00 mL). The low temperature was maintained for 2 h, and then the ice bath was removed and the mixture was stirred for a further 4 h. Water (10 mL) was added, and the mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (150 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (125 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 7% EtOAc-hexane, gave four products corresponding to the expected isomers. The first product was an oil and found to be a mixture of *d*, *l*, and a *meso* compound (two spots TLC R_f = 0.34 and 0.31, 7% EtOAc-hexane but inseparable on a large scale) (0.966 g, 53%). The second product (**100**) was isolated as an oil and was a *meso* compound (0.320 g, 17%): R_f = 0.21; FT-IR ($CHCl_3$ cast) 3600-3200, 1630, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.03 (s, 6 H), 0.10 (s, 12 H), 0.90 (s, 27 H), 1.34-1.1.80 (m, 16 H), 2.02-2.13 (m, 4 H), 2.91 (br s, 2 H), 3.63-3.87 (m, 3 H), 3.93-4.11 (ap qt, J = 6 Hz, 2 H), 4.88-5.06 (m, 4 H), 5.70-5.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.34, -4.10, -3.85, 17.90 (three coincident peaks), 24.74, 25.91, 33.78, 37.45, 43.82, 46.45, 66.94, 70.31, 70.65, 114.59, 138.73; mass (CI) *m/z* calcd for $C_{37}H_{78}O_5Si_3$

686, found 687 (M + 1). Anal Calcd for $C_{37}H_{78}O_5Si_3$: C, 64.66; H, 11.44. Found: C, 64.51; H, 10.75.

6,8,10,12,14-Pentakis[[(1,1-dimethyl)dimethylsilyl-oxy]nonadeca-1,18-diene (101).

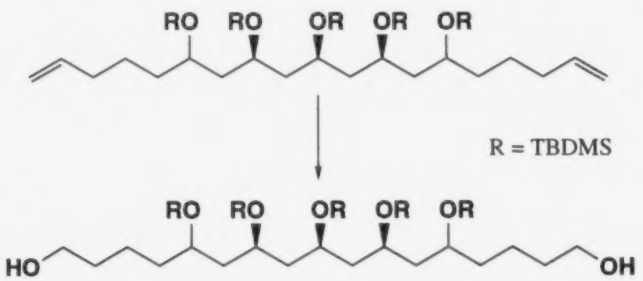


meso isomer

TBDMSCl (1.43 g, 9.52 mmol) and then imidazole (2.37 g, 34.9 mmol) were added to a stirred solution of diol **100** (0.320 g, 0.466 mmol) in CH_2Cl_2 (8.0 mL). The mixture was stirred at room temperature for 20 h, and poured into saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (75 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1% Et_2O-hexane, gave **101** (0.393 g, 92%) as a colorless oil: R_f = 0.20; FT-IR ($CHCl_3$ cast) 3080, 1116, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.02 (s, 6 H), 0.05 (s, 12 H), 0.07 (s, 12 H), 0.89 (ap s, 45 H), 1.18-1.62 (m, 16 H), 2.01-2.15 (m, 4 H), 3.70-3.90 (m, 5 H), 4.91-5.07 (m, 4 H), 5.73-5.93 (m, 2 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.21 (two coincident peaks), -4.16,-3.92, -3.85, 17.95 (two coincident peaks), 18.09, 24.82, 25.77, 26.01 (two coincident peaks), 34.08, 36.65, 46.16, 47.35, 66.91, 66.98, 69.55, 114.55, 138.93; mass (FAB) *m/z* calcd for $C_{28}H_{61}O_3Si_3$ [(M - $C_{21}H_{45}O_2Si_2$) fracture of C-10 to C-11 bond] 529, found 529; *m/z* calcd for $C_{21}H_{45}O_2Si_2$ 385, found 385.

Meso-5,7,9,11,13-Pentakis[[(1,1-methylethyl)dimethylsilyloxy)heptadeca-1,17-diol (102).

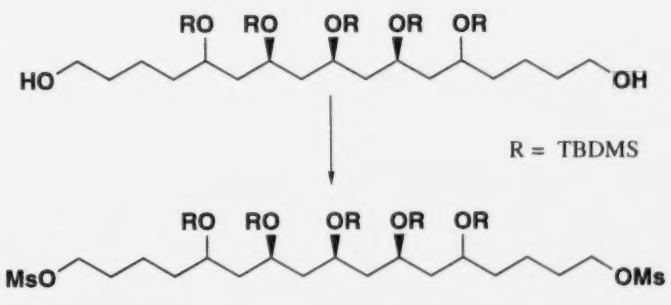


meso isomer

Ozone was bubbled through a cooled (dry ice-acetone) solution of protected pentol **101** (57.3 mg, 62 μmol) in 1:1 MeOH:CH_2Cl_2 (8.0 mL) until a blue color persisted. The excess of ozone was expelled with a stream of Ar, and $NaBH_4$ (0.104 g, 2.74 mmol) was added with stirring. The cold bath was removed and stirring was continued for 2 h. Glacial AcOH (1 mL) was added, and the mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic

phase was separated and washed with brine (75 mL), dried ($MgSO_4$), and evaporated, and the residue was then placed under high vacuum. The waxy semicrystalline product **102** (51.4 mg, 89%), which was not further purified, had: mp 59-63 °C; R_f = 0.28 (20% EtOAc-hexane, silica); FT-IR ($CHCl_3$ cast) 3550-3150, 1111, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.02 (s, 6 H), 0.03 (s, 6 H), 0.05 (ap s, 18 H), 0.90 (ap s, 45 H), 1.20-1.60 (m, 22 H), 3.64 (ap t, *J* = 6 Hz, 4 H), 3.68-3.86 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -4.2 (three coincident peaks), -4.0 (two coincident peaks), 18.0 (three coincident peaks), 21.57, 26.0 (three coincident peaks), 33.1, 36.9, 46.0, 47.2, 62.9, 67.0 (two coincident peaks), 69.5; mass (FAB) *m/z* calcd for $C_{47}H_{107}O_7Si_5$ (M + H) 923, found 923.

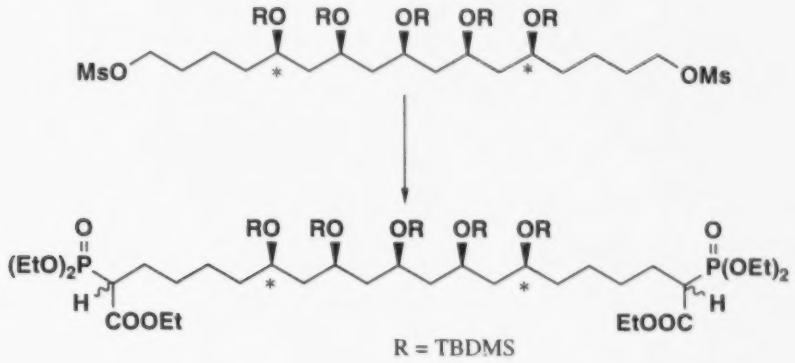
***Meso*-5,7,9,11,13-Pentakis[[(1,1-methylethyl)dimethylsilyloxy)heptadeca-1,17-diol bis(methanesulfonate) (103).**



meso isomer

Triethylamine (1.0 mL, 0.73 g, 7.3 mmol) was added to a stirred and cooled (0 °C) solution of diol **102** (0.208 g, 0.225 mmol) in CH_2Cl_2 (7.0 mL). $MeSO_2Cl$ (90 μL, 0.13 g, 1.2 mmol) was added slowly and the resulting yellow mixture, which gradually turned brown, was stirred for 10 h. The mixture was poured into a mixture of ice (25 mL) and 2 N hydrochloric acid (25 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 30% EtOAc-hexane, gave **103** (0.199 g, 85%) as an oil: R_f = 0.57; FT-IR ($CHCl_3$ cast) 1177, 1113, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.03 (ap s, 12 H), 0.05 (ap s, 18 H), 0.89 (ap s, 45 H), 1.15-1.82 (m, 20 H), 2.89 (s, 6 H), 3.68-3.81 (m, 4 H), 4.21 (ap t, J = 6 Hz, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.28, -4.21, -4.16, -3.95, -3.87, 17.81, 17.86, 17.93, 21.37, 25.83 (two peaks), 25.86, 29.50, 36.58, 37.43, 46.03, 47.25, 65.86, 66.85, 66.87, 69.21, 69.83; mass (FAB) *m/z* calcd for $C_{27}H_{64}O_3Si_3$ 520, found 520 [(M - $C_{22}H_{46}O_8S_2Si_2$) two demesylations and fracture of C-9 to C-10 bond]; *m/z* calcd for $C_{20}H_{32}O_2Si_2$ 360, found 360.

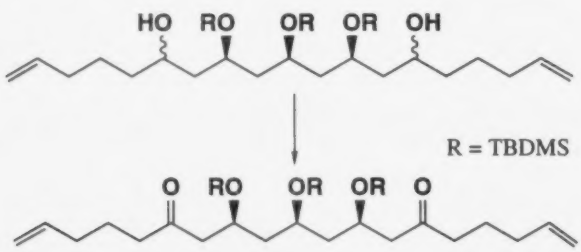
7,9,11,13,15-Pentakis[[(1,1-dimethyl)ethyldimethylsilyl]oxy]-2,20-bis(diethylphosphono)henicosa-1,21-dioic acid, diethyl ester (104).



NaH (9.3 mg, 60% dispersion in mineral oil, 0.24 mmol) was added to a solution of triethyl phosphonoacetate (100 µL, 0.113 g, 0.50 mmol) in dry THF (1.0 mL) and the mixture was stirred for 5 min. The supernatant liquid was added to a solution of bis mesylate **103** (56.4 mg, 54 µmol) and 18-crown-6 (32.5 mg, 123 µmol) in dry THF (1.0 mL) with stirring at room temperature (Ar atmosphere). The mixture was stirred for 1 h and then KI (3 crystals, 1.5 mg) was added. Stirring was continued and the reaction was monitored by TLC (30% EtOAc-hexane, silica). After 1 h, no starting material remained, and the mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (25 mL). The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (25 mL), and brine (2 x 25 mL). The aqueous washes were sequentially back-extracted with the same

portion of EtOAc (25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 20 cm), using 40% EtOAc-hexane, gave **104** (6.2 mg, *ca.* 9%) as an oil: R_f = 0.23; ^1H NMR ($CDCl_3$, 200 MHz, mixture of diastereoisomers[a]) δ 0.03-0.08 (three s, 30 H), 0.87 (ap s, 45 H), 1.10-1.42 (m, 28 H), 1.45-2.10 (m, 16 H), 2.71-2.95 (m, 2 H), 3.57-3.78 (m, 5 H), 4.07-4.32 (m, 10 H) (traces of triethyl phosphonoacetate are present); ^{13}C NMR ($CDCl_3$, 50 MHz, mixture of diastereoisomers[a] *) δ -4.3, -4.0, 16.2, 16.3, 17.6, 21.3, 25.7, 29.4, 29.43, 33.04, 34.4 (d, $^1J_{PC}$ = 133 Hz, 2 C), 46.0, 47.2, 61.5, 62.6 (d, $^2J_{PC}$ = 6 Hz, 4 C) 66.8, 69.1, 69.8, 182.0 (a number of peaks must be coincident).

***Meso*-8,10,12,-Tris[[(1,1-dimethylethyl)dimethylsilyl]-oxy]nonadeca-1,18-dien-6,14-dione (105).**



DMSO (1.10 mL, 1.21 g, 15.5 mmol) was added to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (1.00 mL, 1.46 g, 11.5 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred for

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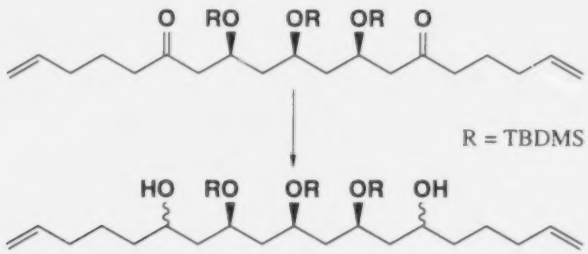
[a] A ^{13}C NMR (125 MHz) indicated isomers were present.

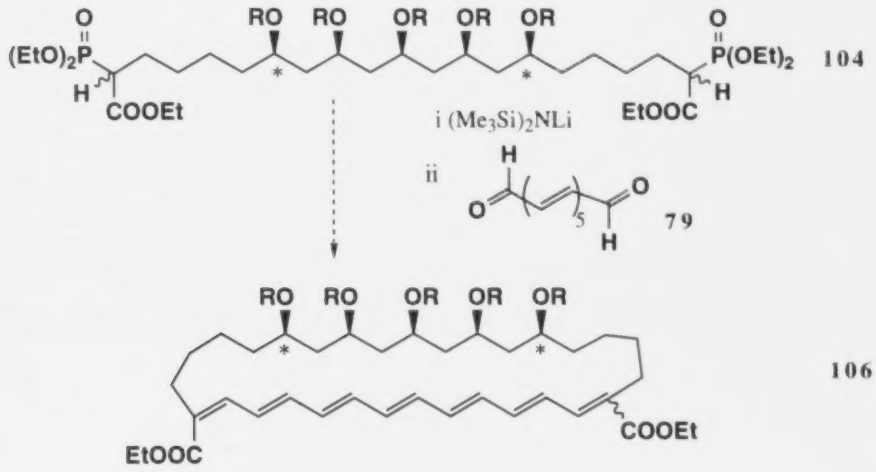
15 min (Ar atmosphere). A solution of isomeric diols **100** (0.527 g, 0.767 mmol) in dry CH_2Cl_2 (20 mL plus 2 x 5 mL as a rinse) was added via cannula, using a positive pressure of Ar, and the reaction mixture was stirred for 30 min. Et_3N (5.00 mL, 3.63 g, 35.87 mmol) was added, the cold bath was removed, and stirring was continued for a further 4 h. Brine (10 mL) was added, and the mixture was poured into 2 N hydrochloric acid (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (2 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 5% EtOAc-hexane, gave **105** (0.376 g, 72%) as a oil: R_f = 0.30; FT-IR ($CHCl_3$ cast) 3080, 1716, 1642, 1113, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ -0.01 (s, 6 H), 0.05 (s, 6 H), 0.08 (s, 6 H), 0.85 (ap s, 18 H), 0.89 (s, 9 H), 1.5-1.7 (m, 8 H), 2.05 (ap q, J = 7 Hz, 4 H), 2.42 (ap t, J = 7.5 Hz, 4 H), 2.55 (ap d, J = 6 Hz, 4 H), 3.75 (ap qt, J = 6 Hz, 1 H), 4.27 (ap qt, J = 6 Hz, 2 H), 4.94-5.09 (m, 4 H), 5.68-5.81 (m, 2 H); ^{13}C NMR ($CDCl_3$. 75 MHz) δ -4.61, -4.37, -4.27, 17.93, 22.45, 25.87, 25.91, 33.08, 43.77, 45.73, 50.23, 66.27, 66.48, 66.73, 115.17, 138.04, 209.23; mass (CI) m/z calcd for $C_{37}H_{74}O_5Si_3$ 682, found 683 (M + 1). Anal Calcd for $C_{37}H_{74}O_5Si_3$: C, 65.06; H, 10.93. Found: C, 64.95; H, 11.21.

8,10,12-Tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-nonadeca-1,18-dien-6,14-diol (100).



$NaBH_4$ (0.340 g, 9.38 mmol) was added to a stirred and cooled (-78 °C) solution of dione **105** (0.376 g, 0.550 mmol) in bench MeOH (20 mL). The cooling bath was left in place, but not recharged, and stirring was continued for 2 h. The mixture was acidified (pH paper) with glacial AcOH and then solid $NaHCO_3$ was added to neutrality (pH paper). The mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 75 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 7% EtOAc-hexane, gave *meso* isomer **100** (0.092 g, 24%), which had spectral data identical to those previously obtained for this compound.

Diethyl 19,21,23,25,27-Pentakis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]cyclohentriconta-1,3,5,7,9,11,13-heptaene-1,14-dicarboxylate (106).



LiHMDS (88 µL, 0.73 N in THF, 64 µmol) was added slowly to a stirred and cooled (-78 °C) solution of bis phosphonate **104** (12.8 mg, 9.75 µmol, i.e. 18.5 mg corrected for 30 mol % of triethyl phosphonoacetate as estimated by ^{1}H NMR) in dry THF (1.0 mL) (Ar atmosphere). The cold bath was removed after 5 min and the mixture was allowed to warm to room temperature. After 1 h, the mixture was diluted to 10 mL with dry THF and taken up into a syringe. A solution of polyene bis aldehyde **79** (5.3 mg, 28 µmol) in dry THF (10 mL) was also placed in a second syringe. Dry THF (5.0 mL) was placed in a dry flask (Ar Atmosphere) and protected from light. (This is important as the product is light sensitive and similar precautions were taken throughout the remainder

of the experiment.) The contents of the syringes were added over 10 h using a syringe pump to the light-protected flask. The mixture was then stirred for an additional 7 h. The mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The aqueous extracts were back-extracted with Et_2O (2 x 25 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by preparative thin layer chromatography over silica gel, using 40% EtOAc-hexane. This procedure gave several bands on the plate. Each band was removed with a razor blade and extracted with Et_2O. The bands of R_f = 0.73 and 0.63 appeared to contain the desired products (**106**). The band at R_f = 0.73 gave one of the isomers of **106** (1.7 mg, 14%) which had: ^1H NMR ($CDCl_3$, 500 MHz) 0.05-0.10 (many s, 30 H), 0.83-0.87 (ap s, 45 H), 0.87-1.80 (hydrocarbon and compound **106**), 2.02-2.10 (m, 4 H), 2.24-2.44 (m, 4 H), 3.85-3.93 (m, 4 H), 4.10-4.17 (5 H), 6.50-6.80 (m, 8 H), 7.32 (d, 2 H). Many peaks in this spectrum are only slightly larger than the ^{13}C coupled satellites of $CDCl_3$, because of the small sample size. Consequently, the integration values are unreliable, but we felt that the positions and peak shapes supported the proposed structure for **106**, on the basis of comparison with spectra obtained by Daroszewski on related compounds.[91] The source of the hydrocarbon contaminant is unknown.

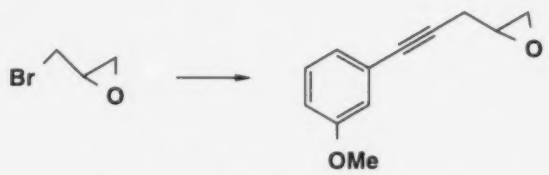
A satisfactory FAB mass spectrum could not be obtained unless the silyl protecting groups were removed. The product

was treated with Bu_4NF in THF to desilylate the substance and the resulting material had: mass (FAB) *m/z* calcd for $C_{37}H_{58}O_9$ 646, found 646; *m/z* calcd for $C_{37}H_{56}O_8$ (M - H_2O) 628, found 628; *m/z* calcd for $C_{35}H_{53}O_8$ (M - OCH_2CH_3) 601, found 601.

The band at R_f = 0.63 gave another isomer of **106** (0.6 mg, 5%) and had: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.05-0.08 (Si-CH_3), 0.88-0.90 (Si*t*-Bu), 1.10-1.60 (aliphatic CH_2 groups), 3.85-3.95 (m, 4 H, OCH_2Me), 4.10-4.40 (m, 5 H, CHOSi), 6.40-6.80 (olefinics), (there may be a peak at 7.30-7.32 , which is obscured by $CHCl_3$ in $CDCl_3$). Again, the small sample size makes the peak areas unreliable, but the chemical shifts and the shapes of the peaks support the proposed structure. A satisfactory FAB mass spectrum could not be obtained unless the silyl protecting groups were removed. The material was treated with Bu_4NF in THF to desilylate the substance and the product had: mass (FAB) *m/z* calcd for $C_{37}H_{58}O_9$ 646, found 646; *m/z* calcd for $C_{37}H_{56}O_8$ (M - H_2O) 628, found 628; *m/z* calcd for $C_{35}H_{53}O_8$ (M - OCH_2CH_3) 601, found 601; *m/z* calcd for $C_{34}H_{53}O_7$ (M - $COOCH_2CH_3$) 573, found 573.

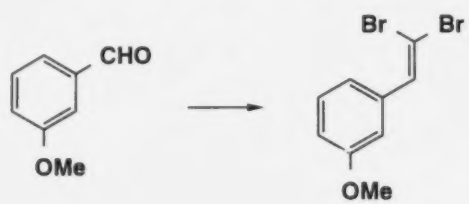
Compounds **73** and **108-113**, are reported in the literature[84]; however, no experimental details or spectral data were available, and so the full experimental procedures are given here.

2-[3-(3-Methoxyphenyl)-2-propynyl]oxirane (108).[84]



Preparation of Starting materials

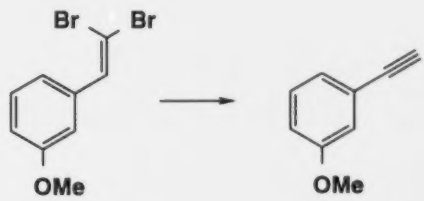
1,1-Dibromo-2-(3-methoxyphenyl)ethene.



Ph_3P (52.50 g, 200 mmol) and Zn (13.10 g, 200 mmol) were added to stirred and cooled (0 °C) CH_2Cl_2 (500 mL) (Ar atmosphere). CBr_4 (66.50 g, 200 mmol) was then added, causing the mixture to reflux slowly. The mixture was stirred for 24 h, the cooling bath being left in place but not recharged, affording a pink mixture. *m*-Anisaldehyde (20.0 mL, 22.4 g, 165 mmol) was added and stirring was continued for 24 h. The solvent was evaporated and the residue was extracted by adding CH_2Cl_2 (100 mL), swirling, adding pentane (400 mL), decanting the supernatant, and evaporating it.[125] This procedure was repeated four times. The residue from the evaporated supernatants was purified by

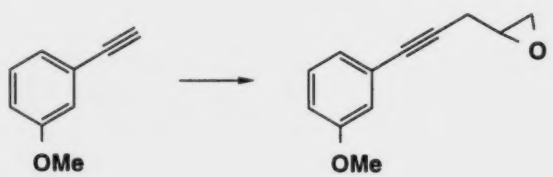
distillation, allowing the recovery of some *m*-anisaldehyde (7.65 g, 56.2 mmol, bp 80 °C, 1.8 Torr), and 1,1-dibromo-2-(3-methoxyphenyl)ethene (29.23 g, 92% after correction for recovered *m*-anisaldehyde): bp 125-126 °C, 1.8 Torr; FT-IR (neat film) 1598, 1577 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3 H), 6.87-6.97 (m, 1 H), 7.05-7.15 (m, 2 H), 7.31 (t, J = 8 Hz, 1 H), 7.49 (ap s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.22, 89.75, 113.63, 114.27, 120.97, 129.36, 136.42, 136.72, 159.40; exact mass *m/z* calcd for $C_9H_8{}^{81}Br_2O$ 293.8901, found 293.8897.

(3-Methoxyphenyl)acetylene.



(3-Methoxyphenyl)acetylene was reported in the supplementary material provided in reference 84; however, it was made by the following (different) method. *n*-BuLi (60 mL, 2.5 N in hexane, 150 mmol) was added to a stirred and cooled (-78 °C) solution of 1,1-dibromo-2-(3-methoxyphenyl)ethene (20.00 g, 68.5 mmol) in dry THF (125 mL) (Ar atmosphere). Stirring was continued for 1 h, and then the cooling bath was removed. After the mixture had warmed to room temperature, saturated aqueous NH_4Cl (20 mL) was added, and then the

mixture was poured into brine.[125] The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Vacuum distillation of the residue through a Vigreux column (10 cm) (50-52 °C, 1 Torr, lit.[84] 63-64 °C, 1.8 Torr), afforded (3-methoxyphenyl)acetylene (7.63 g, 84%) as an oil: FT-IR (neat film) 3290, 3073, 3029, 2109, 1602, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.08 (s, 1 H), 3.81 (s, 3 H), 6.87-6.97 (m, 1 H), 7.00-7.08 (m, 2 H), 7.21-7.31 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.30, 79.50, 83.61, 115.45, 117.04, 123.14, 124.69, 129.44, 159.34; exact mass *m/z* calcd for C_9H_8O 132.0575, found 132.0573.

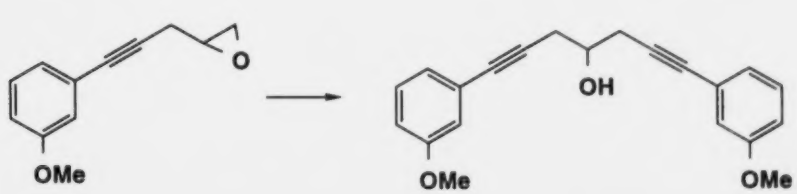


n-BuLi (31.0 mL, 2.5 N in hexane, 78 mmol) was added to a stirred and cooled (-78 °C) solution of (3-methoxyphenyl)-acetylene (9.54 g, 72.2 mmol) in dry THF (100 mL) (Ar atmosphere) and the mixture was stirred for 10 min, affording a pink-red solution. *Freshly* distilled $BF_3 \cdot OEt_2$ (9.55 mL, 77.6 mmol) was added and the mixture was stirred for 10 min, affording an almost colorless solution. Epibromohydrin (6.55 mL, 10.5 g, 77.0 mmol) was added and stirring was continued for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and then the cooling bath removed. The mixture was poured into brine

(100 mL) and the layers were separated. The brine was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated.

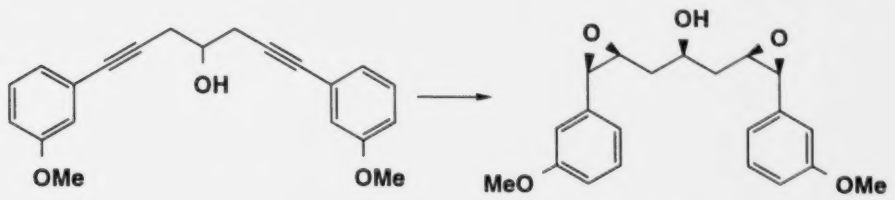
KI (1.00 g, 24.9 mmol) and K_2CO_3 (15.00 g, 109 mmol) were added to a stirred solution of the above bromo hydroxy compound in MeOH (200 mL). The mixture was stirred and monitored by TLC (silica, 15% EtOAc-hexane). After 1 h no α-bromo alcohol was present, and the mixture was filtered and evaporated. The residue was extracted with EtOAc (4 x 50 mL) and the combined extracts were washed with brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (12 x 22 cm), using 20% EtOAc-hexane, gave **108** (6.45 g, 78%, corrected for recovered (3-methoxyphenyl)acetylene, 3.70 g) as an oil: R_f = 0.41; FT-IR (CH_2Cl_2 cast) 3056, 1175, 1165, 1132, 853 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.61-2.72 (m, 2 H), 2.78-2.87 (m, 2 H), 3.16 (m, 1 H), 3.78 (s, 3 H), 6.79-6.89 (m, 1 H), 6.92-7.05 (m, 2 H), 7.18 (ap t, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.21, 46.53, 50.00, 55.25, 82.59, 83.91, 114.64, 116.57, 124.22, 124.28, 129.30, 159.31; exact mass m/z calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0835.

1,7-Bis(3-methoxyphenyl)-1,6-heptadiyn-4-ol (109).[84]



n-BuLi (36.0 mL, 2.5 N in hexane, 90 mmol) was added to a stirred and cooled (-78 °C) solution of (3-methoxyphenyl)-acetylene (11.13 g, 84.22 mmol) in dry THF (350 mL) (Ar atmosphere). After 10 min *freshly* distilled $BF_3 \cdot OEt_2$ (11.1 mL, 12.8 g, 90.3 mmol) was added and the mixture was stirred for 15 min. A solution of epoxide **108** (10.42 g, 55.4 mmol) in THF (20 mL plus 2 mL as a rinse) was added via cannula, and stirring was continued for 30 min. The cooling bath was removed and, after 30 min, saturated aqueous NH_4Cl (20 mL) was added. The mixture was diluted with EtOAc (100 mL) and washed with brine (100 mL). The aqueous layer was extracted with EtOAc (100 mL) and then the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (12 x 20 cm), using 20% EtOAc-hexane, gave **109** (13.34 g, 75%): R_f = 0.15; FT-IR ($CHCl_3$ cast) 3600-3200, 3071, 3029, 1597, 1582, 1175, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.31 (s, 1 H), 2.77-2.87 (m, 4 H), 3.79 (s, 6 H), 4.11 (ap qt, J = 7 Hz, 1 H), 6.81-6.91 (m, 2 H), 6.93-7.07 (m, 4 H), 7.21 (ap t, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.32, 55.30, 68.91, 83.34, 85.30, 114.70, 116.62, 124.22, 124.29, 129.37, 159.36; exact mass *m/z* calcd for $C_{21}H_{20}O_3$ 320.1412, found 320.1416.

(1*S*,7*R*)-1,2:6,7-Dianhydro-3,5-dideoxy-1,7-bis-*C*-(3-methoxyphenyl)-D-*xylo*-heptitol (110).[84]



and isomers (<10%)

A solution of 95% EtOH (60 mL) and ethylenediamine (1.05 mL, 0.944 g, 9.3 mmol) was added via cannula to stirred $Ni(OAc)_2 \cdot 4H_2O$ (3.30 g, 13.3 mmol) in a dry flask that was thoroughly flushed with Ar. Stirring was continued until dissolution was complete (*ca.* 15 min, the solution is a purple color). A solution of $NaBH_4$ (440 mg, 11.6 mmol) in 95% EtOH (25 mL) was added. The addition is accompanied by H_2 evolution and produces a black suspension. After H_2 evolution had ceased, a solution of diyne **109** (3.11 g, 9.71 mmol) in 95% EtOH (60 mL) was added via cannula, using a positive pressure of Ar. The reaction flask was fitted with a large balloon containing H_2 and fitted with a control valve. The Ar atmosphere was removed from the flask using a vacuum line and replaced with hydrogen from the balloon (three times). Then the flask was flushed with hydrogen. The mixture was stirred and monitored by ^1H NMR (80 MHz). Disappearance of the peak at δ 2.3 and appearance of olefinic signals at δ 5.5 and 6.8 were used to assess the progress of

the reaction. After 3.5 h, the reaction flask was opened to the atmosphere and the mixture was evaporated on a rotary evaporator (not quite to dryness). The residue was extracted with $CHCl_3$ (2 x 50 mL) and poured into 2 N HCl (200 mL), causing the black catalyst to decompose and dissolve. The organic phase was washed with brine (100 mL), dried ($MgSO_4$) and evaporated.

The residue was dissolved in dry CH_2Cl_2 (100 mL) and $VO(acac)_2$ (114 mg, 0.328 mmol) was added, followed by *t*-BuOOH (8.00 mL, 3.96 M in CH_2Cl_2, 31.7 mmol). The reaction mixture was stirred for 16 h at room temperature and then water (1 mL) was added, causing the vanadium oxides to precipitate. Celite (5 g) was added and the mixture was filtered through a Celite pad (4 x 5 cm). The pad was washed with CH_2Cl_2 (4 x 100 mL) and the solvent was evaporated. Flash chromatography of the residue over silica (5 x 20 cm), using 40% EtOAc-hexane, gave **110** (830 mg, 24%) as an oil which is a mixture of isomers, mainly (*ca.* 90%, ^1H NMR 300 MHz)* the product shown above: Rf = 0.20; FT-IR ($CHCl_3$ cast) 3600-3200, 1603, 1593, 1157, 1091, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, for major isomer only) δ 1.42-1.55 (m, 4 H), 1.64 (s, 1 H), 3.28-3.85 (m, 2 H), 3.70-3.82 (m, 7 H), 4.02 (d, J = 5 Hz, 2 H), 6.72-7.00 (m, 6 H), 7.18-7.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.11, 55.24, 56.49, 56.94, 68.82, 111.85, 113.42, 118.76,

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* The intensity of the benzylic epoxide hydrogen signals was used to estimate purity. The major product had a doublet at δ 4.02 (integration = 64) and the minor isomers had a multiplet at δ 4.07-4.16 (integration = 5). 64/(5+64)x100%=93% desired compound.

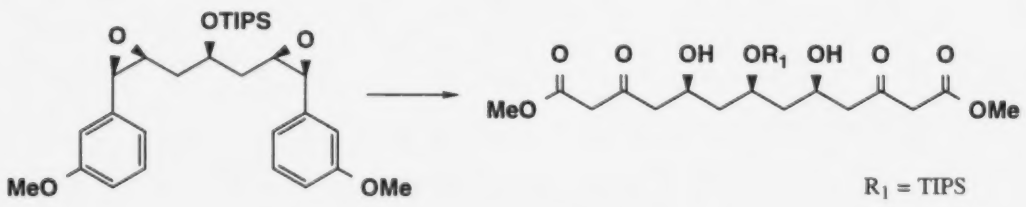
129.30, 136.73, 159.55; exact mass *m/z* calcd for $C_{21}H_{24}O_5$ 356.1624, found 356.1615.

(1*S*,7*R*)-1,2:6,7-Dianhydro-3,5-dideoxy-4-[[(1-methyl)-silyl]oxy]-1,7-bis-*C*-(3-methoxyphenyl)-D-*xylo*-heptitol (111).[84]

Et_3N (3.50 mL, 2.54 g, 25.1 mmol) and then triisopropylsilyl triflate (2.32 mL, 2.63 g, 8.59 mmol) were added to a stirred and cooled (0 °C) solution of bis epoxy alcohol **110** (2.97 g, 7.84 mmol, mixture of isomers >90% desired isomer shown by ^1H NMR estimate) in dry CH_2Cl_2 (20 mL) (Ar atmosphere). The reaction mixture was stirred for 2 h and then solid $NaHCO_3$ (*ca.* 2 g) and solid $MgSO_4$ (*ca.* 5 g) were added. The mixture was filtered through a pad of silica gel (5 x 3 cm). The pad was washed with 40% EtOAc-hexane to remove the desired compound and then the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 10% EtOAc-hexane, gave **111** (2.97 g, 75%) as a mixture of isomers. The material was an oil: R_f = 0.55; FT-IR ($CHCl_3$ cast) 1603, 1594, 1156, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.70-1.30 (m, 21 H), 1.47 (ddd, *J*

= 15, 9, 6 Hz, 2 H), 1.67 (ddd, *J* = 15, 9, 6 Hz, 2 H), 3.28 (ddd, *J* = 9, 6, 6 Hz, 2 H), 3.80 (s, 6 H), 3.99 (d, *J* = 5 Hz, 2 H), 4.07 (m, 1 H), 6.70-7.00 (m, 6 H), 7.20-7.31 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 12.89, 18.36, 34.57, 55.61, 56.37, 57.00, 69.17, 112.34, 113.51, 119.92, 129.62, 137.89, 160.06; exact mass *m/z* calcd for $C_{30}H_{44}O_5Si$ 512.2958, found 512.3686

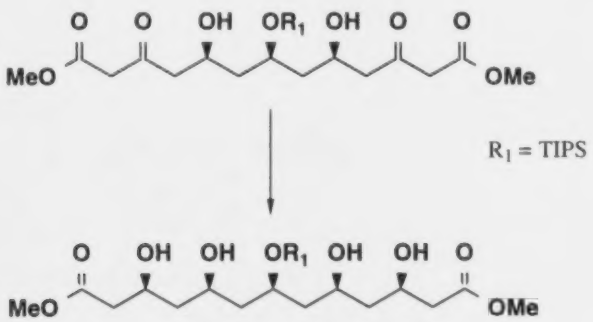
Meso-5,9-Dihydroxy-3,11-dioxo-7-[[tris(1-methylethyl)-silyl]oxy]tridecan-1,13-dioic acid, dimethyl ester (112).[84]



A solution of bis epoxide **111** (0.466 g, 0.909 mmol) in dry THF (5 mL) was added to a stirred and cooled (-78 °C) solution of Li (0.72 g, 0.10 mol) in ammonia (100 mL). The blue solution was stirred for 30 min and then MeOH was added in 1 mL-portions every 5 min until the blue color dissipated. Li (0.35 g, 50 mmol) was then added and the blue color returned. Again, MeOH was added in 1 mL-portions every 5 min until the blue color disappeared. Another portion of Li (0.37 g, 51 mmol) was added and the blue color returned. MeOH (1 mL-portion every 5 min) was added until the blue color disappeared. Solid NH_4Cl was added to quench the

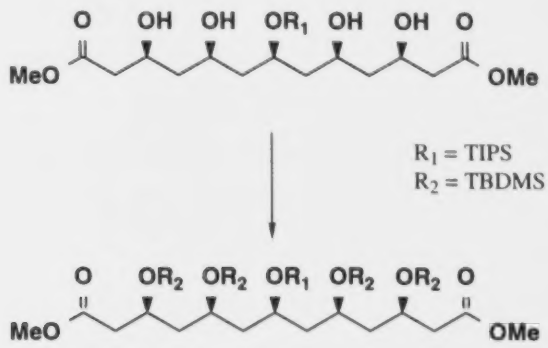
reaction, until vigorous gas evolution ceased and then the ammonia was allowed to evaporate. The solids were extracted with Et_2O (3 x 100 mL) and the ether extracts were filtered and evaporated. The residue was taken up in CH_2Cl_2 (50 mL) and cooled (-78 °C). Ozone was bubbled through the cooled solution until a pale blue color persisted. Oxygen was bubbled through the solution to dissipate the blue color and then dimethyl sulfide (2 mL) was added. Stirring was started, the bath was removed, and stirring was continued overnight. The solvent was evaporated and the residue was dissolved in EtOAc (100 mL) and then washed with water (4 x 25 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 50% EtOAc-hexane, gave **112** (90.0 mg, 20%) as an oil: R_f = 0.19; FT-IR ($CHCl_3$ cast) 3600-3200, 1744, 1715, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.71-1.18 (m, 21 H), 1.32-1.80 (m, 6 H), 2.10-2.45 (m, 1 H), 2.46-2.71 (m, 3 H), 3.20-3.43 (m, 1 H), 3.42-3.51 (m, 3 H), 3.65-3.85 (m, 6 H), 4.05-4.48 (m, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.7, 18.1, 42.7, 49.6, 50.2, 52.4, 65.2, 69.1, 167.3, 203.1; mass (FAB) *m/z* calcd for $C_{24}H_{44}O_9Si$ 504, found 504. Compound **112** appeared to be only one isomer at this stage, as judged by ^1H NMR and ^{13}C NMR spectra.

***Meso*-3,5,9,11-Tetrahydroxy-7-[[tris(1-methylethyl)-silyl]oxy]tridecan-1,13-dioic acid, dimethyl ester (73).**[84]



A solution of Et_2BOMe (0.40 mL, 1.0 M in THF, 0.40 mmol) was added to a stirred and cooled (-78 °C) solution of **112** (90.0 mg, 0.178 mmol) in dry THF (5 mL) and dry MeOH (1 mL) under an Ar atmosphere. Stirring was continued for 20 min and then $NaBH_4$ (20.1 mg, 0.532 mmol) was added. The mixture was stirred for 5 h and then the cooling bath was removed. EtOAc (100 mL) was added and the solution was washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and evaporated. Repeated evaporation from MeOH (6 x 25 mL) gave **73** (90.3 mg, 96% pure by ^1H and ^{13}C NMR spectra): ^1H NMR ($CDCl_3$, 200 MHz) δ 0.80-1.20 (m, 21 H), 1.20-2.00 (m, 12 H), 2.40-2.63 (m, 4 H), 3.60-3.90 (m, 7 H), 3.90-4.20 (m, 2 H), 4.21-4.44 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8, 18.1, 41.6, 43.0, 44.2, 51.7, 68.7, 69.5, 69.7, 172.7. The compound was used without purification for the next step, as advised by the literature procedure.[84]

***Meso*-3,5,9,11-Tetrakis[[(1,1-dimethylethyl)silyl]-oxy]-7-[[tris(1-methylethyl)silyl]oxy]tridecan-1,13-dioic acid, dimethyl ester (113).**[84]

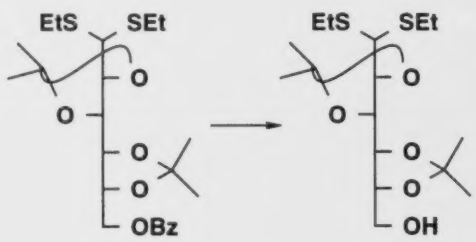


Imidazole (301 mg, 4.42 mmol) and TBDMSCl (292 mg, 1.95 mmol) were added to a stirred solution of **73** (93.3 mg, 0.178 mmol) in dry CH_2Cl_2 (5 mL) under an Ar atmosphere. The mixture was stirred for 3 days and then diluted with CH_2Cl_2 (50 mL), washed with 2 N HCl (25 mL), and water (25 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 7% EtOAc-hexane, gave **113** (53.3 mg, 31%) as an oil: R_f = 0.45; FT-IR ($CHCl_3$ cast) 1743, 1163, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.01 (s, 6 H), 0.02 (s, 6 H), 0.10 (ap s, 12 H), 0.70-0.98 (many s, 36 H), 1.01-1.11 (ap s, 21 H), 1.50-1.80 (m, 8 H), 2.25-2.65 (m, 4 H), 3.65 (s, 6 H), 3.83 (ap qt, J = 7 Hz, 2 H), 3.99 (ap qt, J = 7 Hz, 1 H), 4.22-4.29 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.76, -4.27, -3.94, -2.94, 13.15, 17.86, 18.30, 18.41, 25.70, 42.61, 45.02, 46.27, 46.78, 51.39,

66.69, 67.00, 67.31, 171.94; mass (FAB) *m/z* calcd for $C_{47}H_{101}O_9Si_5$ (M - CH_3) 949, found 949.

Note: There are many small signals near many of the main signals in the ^{13}C NMR spectrum. These are attributed to isomers present in the material.

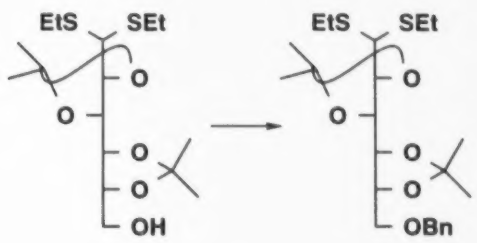
2,3:4,5-Di-*O*-isopropylidene-D-glucose diethyl dithioacetal (118).



Ester **116** (96.4 mg, 0.205 mmol) was dissolved in a solution of NaOH (27.3 mg, 0.701 mmol) in 95% EtOH (2 mL) and stirred at room temperature for 4 h. Water (15 mL) was added and the aqueous suspension was extracted with $CHCl_3$ (3 x 15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and evaporated. The crude material was evaporated from benzene (10 mL) and then placed under high vacuum, affording **118** (61.5 mg, 82%) as an oil: FT-IR ($CHCl_3$ cast) 3600-3200, 1164, 1135, 787 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (2 x ap t, J = 7 Hz, 6 H), 1.37 (s, 3 H), 1.46 (s, 3 H), 1.48 (s, 3 H), 1.52 (s, 3 H), 2.38-2.63 (br s, 1 H), 2.62-2.84 (m, 4 H), 3.76 (ap

d, J = 5 Hz, 2 H), 3.92 (ap d, J = 5 Hz, 1 H), 3.95-4.12 (m, 1 H), 4.18-4.32 (m, 2 H), 4.35-4.49 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.49, 24.94, 26.72, 26.78, 27.18, 27.26, 53.30, 66.90, 71.18, 79.28, 79.50, 109.38, 109.87 (three peaks must be coincident); exact mass m/z calcd for $C_{16}H_{30}O_5S_2$ 366.1535, found 366.1534.

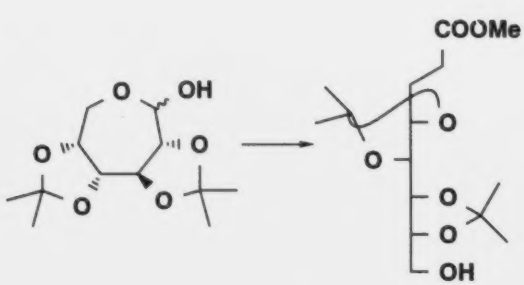
6-*O*-Benzyl-2,3:4,5-di-*O*-isopropylidene-D-glucose diethyl dithioacetal (119).



Benzyl bromide (5.40 mL, 7.72 g, 45.1 mmol) was added to a stirred suspension of NaH [3.05 g, 60% suspension in mineral oil, 76 mmol, previously washed with dry THF (2 x 10 mL) to remove the mineral oil] and **118** (15.35 g, 42.6 mmol) in dry THF (150 mL). The mixture was stirred for 2 h at room temperature but little benzylation occurred (TLC control, silica, 30% EtOAc-hexane). NaI (100 mg) was added and the mixture was refluxed overnight and then cooled to room temperature. Saturated aqueous NH_4Cl (5 mL) was added. The solvent was evaporated and the resulting syrup was dissolved in EtOAc (300 mL). The solution was washed with water (100

mL), saturated aqueous NH_4Cl (10 mL), 2 N hydrochloric acid (10 mL), and water (100 mL). The aqueous washes were back-extracted with EtOAc (100 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (12 x 20 cm), using 30% EtOAc-hexane, gave **119** (9.33 g, 48%): R_f = 0.33; FT-IR ($CHCl_3$ cast) 3062, 3028, 1166, 1131, 1091, 851 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (2 x ap t, *J* = 8 Hz, 6 H), 1.37 (s, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.50 (s, 3 H), 2.63-2.91 (m, 4 H), 3.79 (d, *J* = 8 Hz, 1 H), 3.88 (d, *J* = 8 Hz, 1 H), 4.08 (d, *J* = 9 Hz, 1 H), 4.29-4.71 (m, 6 H), 7.10-7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.28, 14.41, 25.37, 26.59, 27.04, 27.18, 27.27, 52.28, 69.47, 73.64, 75.29, 75.78, 77.67, 79.97, 108.94, 109.75, 127.68, 128.00, 128.37, 138.07 (two peaks must be coincident); exact mass *m/z* calcd for $C_{23}H_{36}O_5S_2$ 456.2004, found 456.2010. There is evidence in the ^{13}C NMR spectrum of a trace contaminant of unknown structure.

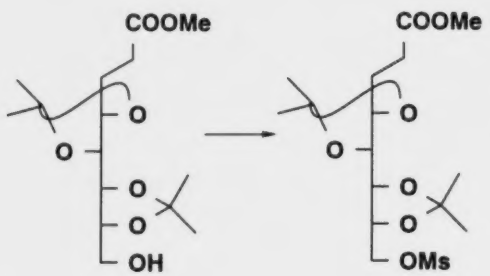
2,3-Deoxy-4,5:6,7-di-*O*-isopropylidene-D-*glucooctanoic* acid, methyl ester (121).



Aqueous NaOH (2 N, 70 mL) was added to a solution of methyl 2-(triphenylphosphonium)acetate bromide (762 mg, 1.84 mmol) in $CHCl_3$ (75 mL) in a separatory funnel. The mixture was shaken gently for 5 min, and the organic phase was dried ($MgSO_4$) and evaporated. Sugar **117** (0.377 g, 1.45 mmol) was dissolved in dry dioxane (10 mL plus 7 mL as a rinse) and added to the ylide. The solution was heated at 90 °C for 3 h and then cooled to room temperature. The dioxane was evaporated and the residue was dissolved in MeOH in an attempt to recrystallize it. The MeOH was evaporated and the crude material was dissolved in EtOAc (10 mL). Pd/C (10%, 100.1 mg) was added and the suspension was placed under a H_2 atmosphere, using a balloon. No hydrogenation was observed. The material was filtered and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 40% EtOAc-hexane, gave the α,β-unsaturated ester (^1H NMR, 80 MHz). This was dissolved in EtOAc (30 mL), 10% Pd/C (95.3 mg) was added, and the suspension was stirred overnight under a H_2 atmosphere (balloon). The catalyst was filtered off and the solvent was evaporated to afford **121** (412 mg, 89%) as an oil: FT-IR ($CHCl_3$ cast) 3500-3150, 1738, 1162, 1136 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 3 H), 1.41 (s, 3 H), 1.42 (s, 3 H), 1.51 (s, 3 H), 1.75-1.88 (m, 1 H), 1.93-2.70 (m, 1 H), 2.39-2.65 (m, 2 H), 2.89 (br s, 1 H), 3.68 (s, 3 H), 3.71 (dd, J = 9, 2 Hz, 1 H), 3.76-3.81 (m, 2 H), 4.08-4.17 (m, 2 H), 4.24-4.32 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.49, 26.45, 26.85, 27.47, 27.51, 30.33, 51.67, 61.53,

74.00, 76.56, 77.51, 78.24, 108.80, 109.56, 173.58; exact mass *m/z* calcd for $C_{14}H_{23}O_7$ (M - CH_3) 303.1444, found 303.1445.

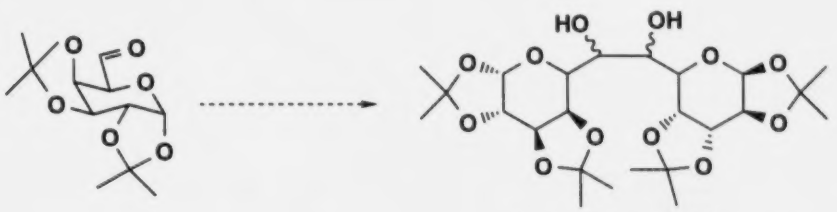
2,3-Dideoxy-4,5:6,7-di-*O*-isopropylidene-8-*O*-methanesulfonyl-D-*glucoo*ctanoic acid, methyl ester (122).



$MeSO_2Cl$ (60 µL, 89 mg, 7.8 mmol) was added to a stirred and cooled (0 °C) solution of **121** (94.1 mg, 0.296 mmol) and Et_3N (1 mL) in dry CH_2Cl_2 (5 mL) (Ar atmosphere). After 3 h, ice was added and the mixture was extracted with CH_2Cl_2 (5 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 x 15 mL) and the aqueous washes were each back-extracted with CH_2Cl_2 (10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered through flash chromatography grade silica gel (2 x 3 cm). The silica was carefully washed with 40% EtOAc-hexane (250 mL), and the pad prevented from running dry. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 30% EtOAc-hexane, gave **122** (112 mg, 95%): R_f = 0.13; mp 83-84 °C; FT-IR ($CHCl_3$ cast) 1735, 1106, 1088, 1074 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.38 (s, 3 H), 1.39 (s, 6 H), 1.51 (s, 3 H), 1.68-2.08 (m, 2 H), 2.34-2.63 (m, 2 H), 3.08 (s, 3 H), 3.60 (dd, *J* = 9, 1 Hz, 1 H), 3.69 (s, 3 H), 4.09 (td, *J* = 8, 4 Hz, 1 H), 4.18 (d, *J* = 8 Hz, 1 H), 4.40-4.56 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.18, 26.46, 26.77, 27.36, 27.54, 30.28, 37.60, 51.62, 69.34, 73.74, 75.12, 75.40, 78.24, 109.52, 109.58 173.50; mass (CI) *m/z* calcd for $C_{16}H_{28}O_9S$ 396, found 397 (M + 1).

Compound (125).



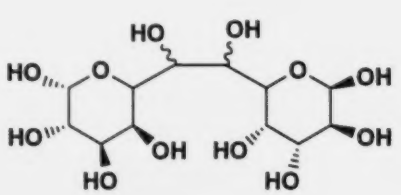
mixture of rearranged isomers of this compound

Method A:

Sodium (1.44 g, 63.8 mmol) was added to a stirred solution of naphthalene (8.05 g, 62.8 mmol) in dry THF (150 mL) (Ar atmosphere). After 2 h, at room temperature, $TiCl_4$ (2.30 mL, 3.98 g, 21.0 mmol) was added over 10 min using a syringe pump.[108] The mixture was refluxed for 30 min and then cooled to room temperature. Aldehyde **124** (0.443 g, 1.72 mmol) in dry THF (10 mL) was added over 10 h using a syringe pump. The mixture was then refluxed for 4 h, cooled to room temperature, and filtered though a Florisil pad (7 x 10 cm).

The filtrate was washed with brine (100 mL), dried ($MgSO_4$), and evaporated. A small sample of the residue (*ca.* 20 mg) was placed under high vacuum with gentle warming at 50 °C to sublime off the naphthalene and leave compound **125**, which had: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.60 (several s, 24 H plus solvent), 3.33-4.00 (m, 8 H), 4.20-4.40 (m, 2 H), 4.55-4.70 (m, 2 H), 5.45-5.60 (m, 2 H).

Residual naphthalene obscured any olefinic signals that might be present in the ^1H NMR spectrum, and so the bulk sample was dissolved in EtOAc (200 mL) and Pd/C (100 mg, 10% Pd) was added. Then the mixture placed in a Parr shaker under H_2 atmosphere (20 psi) for 10 h. The catalyst was filtered off and the solvent was evaporated. A mixture of CH_2Cl_2, water, and CF_3COOH (5:4:1, 10 mL) was added and the mixture was stirred at 0 °C for 2 h. The mixture was diluted with water (25 mL) and CH_2Cl_2 (25 mL) and the layers were separated. The water was evaporated and an ^1H NMR spectrum taken of the deprotected product. The peaks were very broad and no aliphatic methylene signals were observed (no peaks observed below 3 ppm). A mass spectrum was taken and had: mass (CI) *m/z* calcd for $C_{12}H_{22}O_{12}$ 358, found 376 (M + 18). The mass found corresponds to the compound shown below.



Method B:

$TiCl_4$ (3.20 mL, 5.34 g, 29.3 mmol) was added over 10 min to a stirred suspension of Na/Hg amalgam [4.62 g, 39(Na):61(Hg), 45.8 mmol Na] in dry DME (100 mL) which had been previously stirred for 20 min. The black mixture was refluxed for 5 h, and then a solution of aldehyde **124** (443 mg, 1.71 mmol) in dry THF (25 mL) was added via syringe pump over 10 h. Heating was continued at reflux for 4 h after the addition and then the mixture was cooled to room temperature and filtered through a Florisil pad (7 x 10 cm). The pad was washed with Et_2O, the solvent was evaporated, and the residue was dissolved in EtOAc (100 mL). The organic solution was washed with water (3 x 100 mL), dried ($MgSO_4$), and evaporated, to give **125**, which had: ^1H NMR identical to material obtained by method A; ^{13}C NMR ($CDCl_3$, 50 MHz, only most intense signals given) δ 24.3, 24.4, 24.6, 24.8, 24.9, 25.9, 29.6, 63.3, 65.3, 65.6, 66.1, 70.05, 71.6, 72.1, 96.3, 96.5 (many peaks had shoulders).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-methanesulfonyl-α-D-*galacto*pyranose (126).

Et_3N (1.50 mL, 1.82 g, 18.0 mmol) and then $MeSO_2Cl$ (0.40 mL, 592 mg, 5.16 mmol) were added to a stirred and cooled (0 °C) solution of **123** (565 mg, 2.17 mmol) in CH_2Cl_2 (20 mL). After 1.5 h the mixture was poured into CH_2Cl_2 (50 mL) and washed with saturated aqueous $CuSO_4$ (2 x 50 mL), saturated aqueous $NaHCO_3$ (3 x 50 mL), and dried ($MgSO_4$). Evaporation of the solvent, and flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexane, gave **131** (603 mg, 82%) as a solid: R_f = 0.33; mp 106-108 °C (from EtOAc-hexane); FT-IR ($CHCl_3$ cast) 1175, 1146, 1115, 858 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.31 (s, 6 H), 1.42 (s, 3 H), 1.52 (s, 3 H), 3.08 (s, 3 H), 4.07-4.15 (m, 1 H), 4.23 (dd, *J* = 7, 2 Hz, 1 H), 4.31-4.39 (m, 3 H), 4.64 (dd, *J* = 9, 3 Hz, 1 H), 5.52 (d, *J* = 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.8, 24.3, 25.4 (two coincident peaks), 37.3, 65.8, 66.5, 69.8, 70.1 (two coincident peaks), 95.6, 108.4, 109.3; exact mass *m/z* calcd for $C_{12}H_{19}O_8S$ (M - CH_3) 323.0801, found 323.0837.

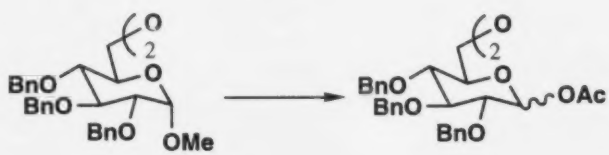
Di[methyl 2,3,4-tri-*O*-benzyl-α-D-*glucopyranoside*] 6',6-anhydride (132).

Et_3N (9.0 mL, 6.5 g, 64 mmol) and then $MeSO_2Cl$ (2.50 mL, 3.70 g, 32.3 mmol) were added to a stirred and cooled (0 °C)

solution of monosaccharide **129** (3.73 g, 8.03 mmol) in dry CH_2Cl_2 (50 mL) (Ar atmosphere). After 1 h, the mixture was poured into a separatory funnel. CH_2Cl_2 (50 mL) was added and the mixture was washed with saturated aqueous $NaHCO_3$ (3 x 50 mL), dried ($MgSO_4$), and evaporated. In a second flask, KH (1 g, 35% suspension in mineral oil, 9 mmol) was washed with THF (2 x 10 mL). A solution of monosaccharide **129** (3.54 g, 7.62 mmol) and 18-crown-6 (7.77 g, 29.3 mmol) in THF (20 mL plus 5 mL as a rinse) was added to the KH, using a cannula and a positive pressure of Ar. A little more KH (0.1 g, 35% in mineral oil, 0.9 mmol) was added, as the solid disappeared (an excess of KH is desirable). The suspension was stirred for 10 min, producing a dark green color. The previously prepared mesylate (**131**) was dissolved in dry THF (10 mL plus 5 mL as a rinse) and added via cannula to the deprotonated sugar mixture. After 8 h, the reaction mixture was poured into a separatory funnel and diluted with EtOAc (100 mL). The mixture was washed with water (100 mL) and brine (5 x 75 mL) (addition of some hexane helped to break the emulsion that formed). The washes were each sequentially back-extracted with EtOAc (50 mL) and $CHCl_3$ (2 x 75 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 25% EtOAc-hexane, gave **132** (2.55 g, 36%) as an oil: R_f = 0.33; $[\alpha]_D$ = +35° (c 2.4, $CHCl_3$); FT-IR ($CHCl_3$ cast) 3063, 3030, 1162, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.03 (s, 6 H), 3.46 (dd, J = 11, 4 Hz, 2 H), 3.51-3.80 (m, 8

H), 3.96 (ap t, J = 9 Hz, 2 H), 4.51-4.99 (m, 14 H), 7.20-7.43 (m, 30 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.12, 70.50, 70.53, 73.42, 75.00, 75.82, 77.49, 80.17, 82.14, 98.03, 127.62, 127.68, 127.88, 128.04, 128.10, 128.42, 128.48, 138.27, 138.54, 138.89 (some of the aromatic carbon signals are coincident); mass (FAB) m/z calcd for $C_{56}H_{62}O_{11}$ 910, found 910. Anal Calcd for $C_{56}H_{62}O_{11}$: C, 73.81; H, 6.86. Found: C, 73.90; H, 7.08.

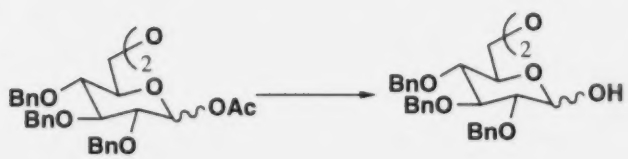
Di[2,3,4-tri-*O*-benzyl-D-*glucopyranosyl* acetate] 6',6-anhydride (133).



Anhydride **132** (90 mg, 0.098 mmol) was dissolved in 1:5 TFA:Ac_2O[110] and the solution was stirred at room temperature for 4 h. The solution was then evaporated from toluene (2 x 25 mL). The residue was dissolved in EtOAc (50 mL) and washed with water (100 mL) and saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and evaporated. The residue was evaporated again from toluene (25 mL). Flash chromatography of the residue over silica gel (1 x 20 cm), using 30% EtOAc-hexane, gave **133** (56.1 mg, 58%) as an oil: R_f = 0.38; FT-IR ($CHCl_3$ cast) 3063, 3030, 1155, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, mixture of isomers) δ 2.12 (ap s, 6 H), 3.47-3.98 (m, 12

H), 4.53-4.85 (m, 13 H), 6.29 (ap d, J = 3 Hz, 1 H, α anomeric), 7.11-7.45 (m, 30 H); ^{13}C NMR ($CDCl_3$, 125 MHz, mixture of isomers) δ 21.09, 69.56, 69.89, 73.23, 73.28, 75.24, 75.72, 76.87, 79.14, 81.25, 81.59, 81.63, 85.63, 89.87, 127.46, 127.60, 127.64, 127.74, 127.81, 127.89, 127.95, 127.95, 127.99, 128.17, 128.23, 128.39, 128.45, 128.88, 137.55, 137.58, 137.64, 138.19, 138.54, 138.61, 169.44 (many peaks must be coincident); mass (FAB) *m/z* calcd for $C_{58}H_{62}O_{13}$ 966, found 966. The ^1H NMR spectrum indicates that the compound appears to be about a 1:1:1:1: mixture of the four possible anomers.

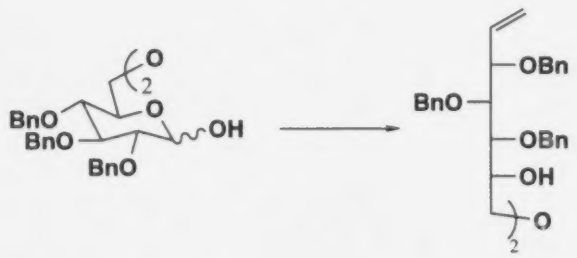
Di[2,3,4-tri-*O*-benzyl-D-*glucopyranose*] 6',6-anhydride (134).



Anhydride **133** (351 mg, 0.363 mmol) was dissolved in a mixture of water (10 mL), triethylamine (10 mL), and MeOH (20 mL).[111] The solution was stirred at room temperature for 5 h, poured into EtOAc (100 mL), and washed with water (2 x 50 mL), saturated aqueous $CuSO_4$ (100 mL), and brine (50 mL). The aqueous washes were each sequentially back-extracted with EtOAc (50 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated, to afford **134** (319 mg, 99%) as an

oil: FT-IR ($CHCl_3$ cast) 3500-3200, 3030, 1144, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.17-3.66 (m, 10 H), 3.71-4.11 (m, 4 H), 4.55-4.98 (m, 13 H), 5.03-5.12 (m, 1 H), 7.13-7.33 (m, 30 H); ^{13}C NMR (CD_2Cl_2, 75 MHz, mixture of isomers) δ (major signals only) 70.58, 70.70, 71.02, 73.26, 74.84, 75.02, 75.16, 75.78, 78.30, 78.38, 80.76, 81.84, 83.64, 84.84, 91.30, 97.62, 127.59, 127.83, 127.96, 128.02, 128.20, 128.24, 128.29, 128.41, 128.61, 128.69, 128.76, 130.09, 138.56, 138.99; 139.39 (many signals must be coincident); mass (FAB) *m/z* calcd for $C_{54}H_{58}O_{11}$ 882, found 882.

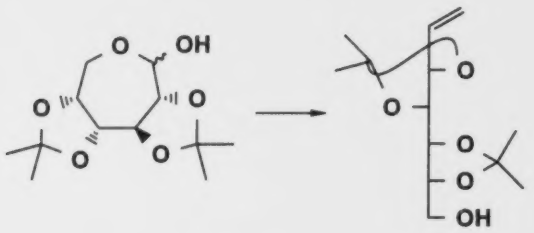
Di[3,4,5-tri-*O*-benzyl-6,7-dideoxy-L-6-*gulo*heptenitol] 1',1-anhydride (135).



n-BuLi (180 μL, 1.6 N in hexane, 0.29 mmol) was added to a stirred suspension of methyltriphenylphosphonium bromide (100 mg, 0.281 mmol) in dry DME (3.0 mL), affording a yellow solution (Ar atmosphere). In a second flask, *n*-BuLi (30 mL, 1.6 N in hexane, 0.048 mmol) was added to a stirred solution of disaccharide **134** (39.6 mg, 0.0448 mmol) in dry DME (1.0 mL) and, after 20 min, the ylide solution was added via

cannula, using a positive pressure of Ar. The mixture was warmed to 45 °C and monitored by TLC (silica, 50% EtOAc-hexane). After 2 h, water (5 mL) and EtOAc (75 mL) were added and the mixture was washed with water (50 mL) and brine (50 mL). The aqueous washes were each sequentially back-extracted with EtOAc (25 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 mm x 20 cm), using 50% EtOAc-hexane, gave **135** (5.0 mg, 12%) as an oil: R_f = 0.56; FT-IR ($CHCl_3$ cast) 3600-3200, 3063, 3029, 1089, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30-1.80 (br s, 2 H), 3.43-3.52 (m, 2 H), 3.53-3.61 (m, 4 H), 3.85-3.96 (m, 2 H), 4.12 (ap t, *J* = 7 Hz, 2 H), 4.24-4.81 (m, 14 H), 5.13-5.27 (m, 4 H), 5.64-5.87 (m, 2 H), 7.10-7.45 (m, 30 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.21, 70.62, 73.15, 74.93, 75.74, 77.47, 78.04, 80.19, 127.62, 127.68, 127.76, 127.87, 127.96, 128.02, 128.14, 128.40, 128.45, 128.50, 137.93, 138.18, 138.31, 138.60, 138.74 (some aromatic and olefinic peaks must be coincident); mass (FAB) *m/z* calcd for $C_{56}H_{63}O_9$ (M + H) 879, found 879.

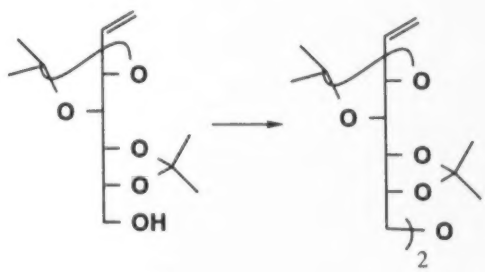
6,7-Dideoxy-2,3:4,5-di-*O*-isopropylidene-L-6-*gulo*hep-tenitol (136).



n-BuLi (0.67 mL, 1.6 N in hexane, 1.1 mmol) was added to a stirred and cooled (-78 °C) suspension of methyltriphenyl-phosphonium bromide (373 mg, 1.04 mmol) in dry THF (5 mL) (Ar atmosphere). After the addition the bath was removed and the reaction mixture was allowed to warm to room temperature. *n*-BuLi (0.27 mL, 1.6 N in hexane, 0.45 mmol) was added to a stirred and cooled (0 °C) solution of monosaccharide **117** (113 mg, 0.434 mmol) in dry THF (4 mL) (Ar atmosphere). After 2 min the yellow ylide solution was added via cannula, using a positive pressure of Ar, and the cooling bath was removed. The reaction was monitored (TLC control, silica, 40% EtOAc-hexane). No reaction was noted and so the mixture was heated to 45 °C. After 1 h at this temperature reaction was complete, and the mixture was quenched with water (1 mL), poured into EtOAc (50 mL), and washed with water (2 x 50 mL). The aqueous washes were each sequentially back-extracted with EtOAc (25 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 40% EtOAc-hexane, gave **136**

(84.0 mg, 75%) as an oil: R_f = 0.25; $[\alpha]_D$ = -28° (c 0.92, $CHCl_3$); FT-IR ($CHCl_3$ cast) 3600-3200, 1166, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.37 (s, 3 H), 1.43 (s, 6 H), 1.52 (s, 3 H), 2.67 (br s, 1 H), 3.70 (dd, *J* = 9, 2 Hz, 1 H), 3.77 (ap d, *J* = 6 Hz, 2 H), 4.07 (dd, *J* = 8, 2 Hz, 1 H), 4.25 (dt, *J* = 8, 6 Hz, 1 H), 4.48 (ap t, *J* = 9 Hz, 1 H), 5.24-5.49 (m, 2 H), 5.71-5.88 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.57, 26.50, 26.90, 27.25, 61.51, 73.47, 77.41, 78.34, 79.37, 108.89, 109.89, 119.99, 134.60; exact mass *m/z* calcd for $C_{13}H_{22}O_5$ 258.1467, found 258.1465. Anal Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.28; H, 8.73.

Di[6,7-dideoxy-2,3:4,5-di-*O*-isopropylidene-L-6-*gulo*heptenitol] 1',1-anhydride (137).



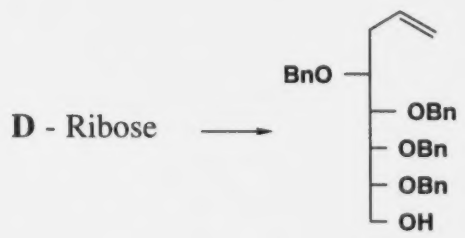
Et_3N (1.00 mL, 0.73 g, 7.3 mmol) and then $MeSO_2Cl$ (225 µL, 333 mg, 2.90 mmol) were added to a stirred and cooled (0 °C) solution of monosaccharide **136** (248 mg, 0.962 mmol) in dry CH_2Cl_2 (5.00 mL) (Ar atmosphere). After 30 min the mixture was poured into a separatory funnel containing CH_2Cl_2 (50 mL). The solution was washed with water (25 mL),

saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), and dried ($MgSO_4$). The mixture was filtered through flash chromatography grade silica (3 x 5 cm) and the pad was washed with 20% EtOAc-hexane (5 x 20 mL). Evaporation of the filtrate afforded the crude mesylate, which was used without further purification, as a solution in dry THF (5 mL).

A second portion of the monosaccharide **136** (162 mg, 0.628 mmol) and 18-crown-6 (627 mg, 2.38 mmol) were dissolved in dry THF (4 mL plus 2 mL rinse) (Ar atmosphere) and added to a flask containing KH (337 mg, 35% suspension in mineral oil, 2.94 mmol) (Ar atmosphere) which had been washed with dry THF (2 x 5 mL) via cannula using a positive pressure of Ar. The reaction mixture was stirred for 10 min at room temperature and then cooled (0 °C). The mesylate solution was then added via cannula using a positive pressure of Ar, and the flask was rinsed with THF (2 mL). The reaction mixture was stirred for 3 h at 0 °C and then water (3 mL) was added. The mixture was poured into EtOAc (50 mL), and the mixture was washed with water (50 mL), and the water back-extracted with EtOAc (3 x 25 mL). Each organic extract was sequentially washed with the same portion of brine (25 mL). The combined organic extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 15% EtOAc-hexane and then 20% EtOAc-hexane, gave **138** (55.2 mg, 17%) as an oil: R_f = 0.23; FT-IR ($CHCl_3$ cast) 1167, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38 (s, 6 H), 1.40 (s, 6 H), 1.42 (s, 6 H), 1.53 (s, 6 H), 3.57

(dd, J = 8, 2 Hz, 2 H), 3.83 (ap d, J = 7 Hz, 4 H), 4.08 (dd, J = 9, 2 Hz, 2 H), 4.29-4.50 (m, 4 H), 5.21-5.49 (m, 4 H), 5.68-5.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.4, 26.6, 26.7, 27.2, 63.8, 73.4, 75.0, 78.7, 79.0, 109.4, 109.7, 119.5, 134.7; mass (CI) m/z calcd for $C_{26}H_{42}O_9$ 498, found 516 (M + 18).

2,3,4,5-Tetra-*O*-benzyl-6,7,8-trideoxy-D-*talo*-7-octenitol (141).



Sn (7.92 g, 325 mesh, 66.7 mmol) and then allyl bromide (8.50 mL, 12.16 g, 100 mmol) were added to a solution of D-ribose (5.00 g, 33.3 mmol) in 9:1 EtOH:water (530 mL),[90] and the mixture was refluxed and monitored by TLC [silica, a mixture of butanol (4), acetone (5), water (1)]. After 10.5 h the mixture was cooled to room temperature, neutralized with 6 N NaOH (pH paper), and filtered through a pad of Celite (5 x 5 cm). The filtrate was evaporated, and the residue was then evaporated from EtOH (2 x 100 mL) and then from benzene (100 mL) and, finally, placed under high vacuum, to afford the chain-extended product, which was contaminated

by tin species. (A 100 mg sample was saved for ^{1}H NMR measurements).

Ph_3CCl (9.15 g, 32.8 mmol) was added to a solution of the crude chain-extended product in dry pyridine (120 mL) (Ar atmosphere), and the mixture was heated at 100 °C for 1 h and then cooled to room temperature. The pyridine was evaporated and saturated aqueous $NaHCO_3$ (200 mL) was added. The aqueous mixture was extracted with $CHCl_3$ (3 x 150 mL) and each organic extract was sequentially washed with water (3 x 100 mL). The organic solution was dried ($MgSO_4$) and evaporated. The residue was evaporated three times from benzene (3 x 100 mL), to remove all traces of pyridine, and then placed under high vacuum overnight. This procedure afforded the crude 1-*O*-trityl-protected sugar. (A 100 mg sample was taken for ^{1}H NMR measurements.)

NaH (20 g, 80% suspension in mineral oil, 0.66 mol) was added to a stirred solution of the above trityl compound in dry DMF (400 mL). After 1 h, the mixture was cooled to 0 °C, and benzyl bromide (75 mL, 0.11 kg, 0.65 mol) was added dropwise over 1 h. The cold bath was removed and stirring was continued for 14 h. The excess of NaH was destroyed by addition of MeOH (50 mL) and then the mixture was poured into a separatory funnel containing water (500 mL), and extracted with CH_2Cl_2 (3 x 125 mL). The combined extracts were washed with water (5 x 100 mL). The water washes were each sequentially back-extracted with CH_2Cl_2 (100 mL). Then the organic extracts were combined, dried ($MgSO_4$), and evaporated

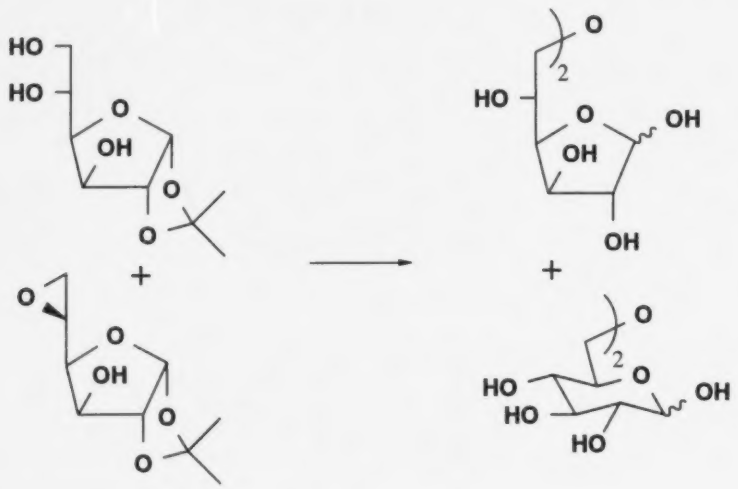
at 60 °C, using first an aspirator and then an oil pump to remove the excess of BnBr. The residue was evaporated three times from benzene (3 x 100 mL), and then finally under oil pump vacuum. This procedure afforded the fully protected sugar.

The fully protected sugar was dissolved with stirring in 4% H_2SO_4 in MeOH (400 mL) at room temperature. After 1 h, water (500 mL) was added and the mixture was extracted with EtOAc (4 x 250 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$), and evaporated, to afford the crude tetrabenzyl-protected sugar.

The material was purified in several steps. Flash chromatography over silica gel (7 x 25 cm), using 20% EtOAc-hexane, gave two fractions. One fraction (4.82 g) was apparently pure, and the second fraction (1.85 g) was a mixture of diastereoisomers. Flash chromatography of the first fraction was repeated four times over silica gel (4 x 20 cm), using 0.5% MeCN-$CHCl_3$. The same column was used for the first three times, and, in each case, the mixed fractions were set aside. This procedure afforded the desired diastereoisomer **141** (2.60 g, 14%). The material appears to be very largely (> 90%, ^1H NMR estimate) the desired isomer and had: FT-IR ($CHCl_3$ cast) 3600-3200, 3087, 3063, 3030, 1093, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.16-2.57 (m, 3 H), 3.67-3.98 (m, 6 H), 4.50-4.85 (m, 8 H), 4.96-5.13 (m, 2 H), 5.71-5.93 (m, 1 H), 7.22-7.48 (m, 20 H); ^{13}C NMR ($CDCl_3$, 75

MHz) δ 35.78, 61.29, 71.93, 72.95, 73.15, 74.88, 79.05, 79.29, 79.43, 81.72, 117.45, 127.50, 127.57, 127.77, 127.88, 127.92, 128.29, 128.44, 134.52, 138.16, 138.63, 138.79 (some aromatic peaks must be coincident); mass (FAB) *m/z* calcd for $C_{36}H_{41}O_5$ (M + H) 553, found 553.

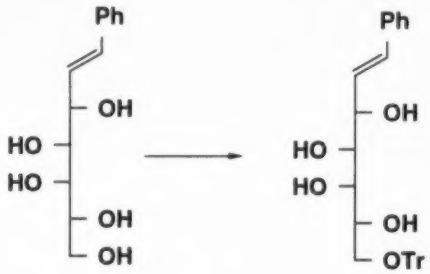
Di[D-glucose] 6',6-anhydride (146).[85]



Compound **75** (2.31 g, 10.5 mmol) and monosaccharide **76** (1.55 g, 7.67 mmol) were mixed together and placed under an Ar atmosphere. The mixture was heated at 160 °C for 3.5 h. Any **75** that sublimed was returned to the melt using a heat gun. The mixture was then cooled to room temperature, at which point it solidified. Aqueous AcOH (50%, 50 mL) was added, the mixture was heated at 80 °C for 5 h, cooled to room temperature, and evaporated. Traces of AcOH were removed by evaporation from toluene (3 x 100 mL). The

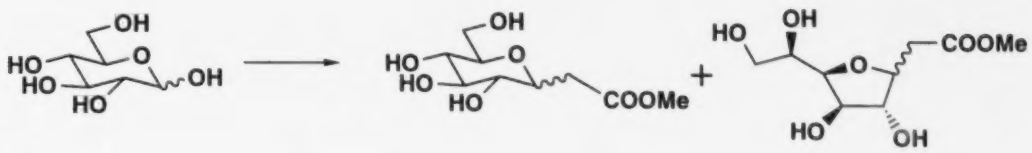
carbohydrate mixture was taken up in water (40 mL) and the mono- and disaccharides were separated on a carbon column as follows. The column was prepared by slurrying a 1:1 (w/w) mixture of carbon (*ca.* 30 g, 60-200 mesh) and Celite (*ca.* 30 g) with water. The monosaccharides are eluted with 2% EtOH-water (*ca.* 1 L), and the disaccharides with 10% EtOH-water. This procedure afforded the **146** (793 mg, 30%), which was purified by dissolution in MeOH and precipitation with Et_2O. This precipitation must be done with care, as traces of acid will result in glycoside formation. Alternatively, the sugar can be dissolved in water (1 g/10 mL) and the solvent removed by lyophilization, to afford crystalline material: mp 96-100 °C (no mp given in lit.[85]); FT-IR ($CHCl_3$ cast) 3600-3000, 1042 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 3.2 (t), 3.25-3.6 (m), 3.6-4.15 (m), 4.15-4.45 (m), 4.61 (d, J = 6 Hz, 1 H, β anomeric), 5.72 (d, J = 2 Hz, 1 H, α anomeric). The spectrum was impossible to integrate satisfactorily because the peaks were too broad and virtually all were overlapping; ^{13}C NMR (DMSO-d_6, 75 MHz, only major peaks reported) δ 48.54,, 61,19, 70.27, 70.58, 70.81, 71.26, 71.53, 71.90, 72.195, 73.03, 74,66, 74.66, 74.79, 75.12, 76.63, 76.71, 92.12, 96.74, 96.86; mass (FAB) *m/z* calcd for $C_{12}H_{23}O_{11}$ (M + H) 343, found 343.

(*E*)-6,7-Dideoxy-7-phenyl-1-*O*-triphenylmethyl-L-6-*galacto*heptenitol (149).



Ph_3CCl (124 mg, 0.445 mmol) was added to a stirred solution of monosaccharide **148** (101 mg, 0.398 mmol) in dry pyridine (5 mL) (Ar atmosphere). The mixture was heated at 100 °C for 2 h, cooled to room temperature, and evaporated. Traces of pyridine were removed by evaporation from benzene (20 mL), and flash chromatography of the residue over silica gel (2 x 20 cm), using 90% EtOAc/CH_2Cl_2, gave **149** (158 mg, 88%) as an oily solid: R_f = 0.46; FT-IR ($CHCl_3$ cast) 3600-3200, 3082, 3060, 3025 1073, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.35-3.10 (m, 4 H), 3.24 (dd, *J* = 11, 6 Hz, 1 H), 3.37 (dd, *J* = 11, 6 Hz, 1 H), 3.64 (s, 2 H), 3.99 (ap t, *J* = 5 Hz, 1 H), 4.46 (dd, *J* = 7, 2 Hz, 1 H), 6.21 (dd, *J* = 17, 7 Hz, 1 H), 6.60 (d, *J* = 17 Hz, 1 H), 7.10-7.40 (m, 20 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.11, 69.73, 72.01, 72.28, 74.33, 87.40, 126.64, 127.32, 127.92, 128.51, 128.62, 132.26, 136.43, 143.55 (several aromatic peaks must be coincident).

Methyl 2-(D-*Gluco*pyranosyl)acetate and Methyl 2-(D-*Gluco*furanosyl)acetate (151).



Aqueous NaOH (2 N, 25 mL) was added to a solution of methyl 2-(triphenylphosphonium)acetate bromide (4.30 g, 10.4 mmol) in $CHCl_3$ (25 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry dioxane (25 mL), and D-glucose (1.81 g, 10.0 mmol) was added. The mixture was then heated at 95 °C for 6 h, care being taken not to exceed this temperature. The mixture was cooled to room temperature and then evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (50 mL). The layers were separated and the water was extracted with CH_2Cl_2 (1 x 50 mL). The aqueous phase was evaporated and an attempt was made to crystallize the residue from EtOH, which afforded some glucose (153 mg, 0.85 mmol). Evaporation of the mother liquor gave **151** (1.98 g, 92%) as a syrup: FT-IR (neat film) 3600-2700, 1778, 1732, 1138, 1070 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.10-2.50 and 2.55-2.97 (m, 2 H, CH_2 α to esters,), 3.07 (s with shoulders, 3 H, $COOCH_3$), 3.15-3.75 (m, 7 H, C**H**OH), 3.76-5.20 (m, 4 H, OH); ^{13}C NMR (DMSO-d_6, 75 MHz, major isomer marked with *) δ 48.68*, 51.31* (shoulder),

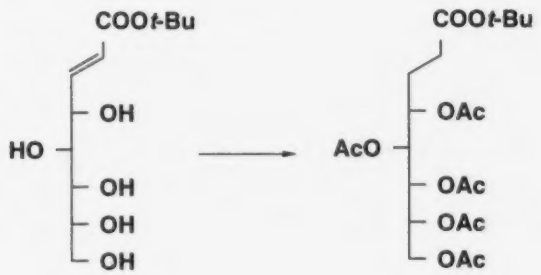
51.39, 61.00, 61.13, 63.69*, 63.89, 68.52*, 69.47, 69.68, 70.19, 70.23, 70.67, 72.50*, 72.96, 73.34, 73.45, 74.37, 76.40*76.53, 76.59, 76.71, 79.86, 80.42, 80.52*, 80.87, 81.27, 82.03, 87.53*, 171.36, 171.67, 171.73, 176.20*; mass (CI) *m/z* calcd for $C_9H_{16}O_7$ 236, found 254 (M + 18).

2,3-Dideoxy-D-*gluco*-2-octenoic acid, 1,1-dimethylethyl ester (152).

Aqueous NaOH (2 N, 25 mL) was added to a solution of *t*-butyl 2-(triphenylphosphonium)acetate bromide (4.70 g, 10.3 mmol) in $CHCl_3$ (25 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry dioxane (25 mL), and D-glucose (1.81 g, 10.0 mmol) was added. The mixture was then heated at 95 °C for 3 h, care being taken not to exceed this temperature. The mixture was cooled to room temperature and then evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (50 mL). The layers were separated and the water was extracted with CH_2Cl_2 (1 x 50 mL). The aqueous phase was evaporated and the residue was recrystallized from MeOH, affording **152** (1.84 g, 66%): mp 157-158 °C; $[\alpha]_D$ = -16° (c 0.82, water); FT-IR (nujol mull) 3600-2800, 1689, 1653, 1153 cm^{-1}; ^1H NMR (D_2O,

300 MHz) δ 1.51 (s, 9 H, $C(CH_3)_3$), 3.54-3.66 (m, 2 H), 3.72-3.88 (m, 3 H), 4.41-4.47 (m, 1 H, H-4), 6.08 (dd, *J* = 17, 2 Hz, 1 H, H-2), 6.86 (dd, *J* = 17, 7 Hz, 1 H, H-3); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 27.8 (q', $C(CH_3)$, 63.3 (t', C-8), 70.8 (d'), 71.2 (d'), 71.9 (d'), 72.3 (d'), 79.5 (s', CMe_3), 121.5 (d', C-2), 148.4 (d', C-3), 165.2 (s', C-1); mass (CI) *m/z* calcd for $C_{12}H_{22}O_7$ 278, found 296 (M + 18). Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 51.55; H, 7.94.

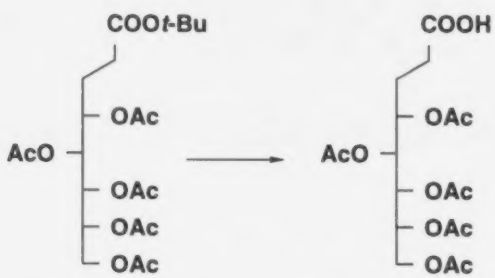
4,5,6,7,8-Penta-*O*-acetyl-2,3-dideoxy-D-*glucooctanoic* acid, 1,1-dimethylethyl ester (153).



Pd/C (10%, 50 mg) was added to a solution of monosaccharide **152** (250 mg, 0.899 mmol) in MeOH (20 mL). The mixture was placed in a Parr shaker under a hydrogen atmosphere of 50 psi. After 4 h the mixture was filtered and the solvent was evaporated. The residue was dissolved in dry pyridine (20 mL) (Ar atmosphere) and then Ac_2O (7 mL) was added. The reaction mixture was stirred at room temperature for 16 h and then evaporated. Traces of pyridine were removed by evaporation from toluene (2 x 10 mL) and the

residue was recrystallized from hexane, giving **153** (372 mg, 83%): mp 94 °C; $[\alpha]_D$ = +2.3° (c 1.8 $CHCl_3$); FT-IR ($CHCl_3$ cast) 1750, 1156, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9 H), 1.61-1.84 (m, 1 H), 1.88-2.01 (m, 1 H), 2.01-2.10 (4 x s, 12 H), 2.14 (s, 3 H), 3.02 (ap t, *J* = 7 Hz, 2 H), 4.11 (dd, *J* = 13, 6 Hz, 1 H), 4.24 (dd, *J* = 13, 4 Hz, 1 H), 5.01-5.15 (m, 2 H), 5.25 (dd, *J* = 8, 4 Hz, 1 H), 5.43 (dd, *J* = 8, 4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.58, 20.75 (two coincident peaks), 20.82 (two coincident peaks), 25.74, 28.10, 30.71, 61.61, 68.69 (two coincident peaks), 70.65, 71.03, 80.70, 169.84, 169.96, 170.00, 170.28, 170.58, 171.55; mass (FAB) *m/z* calcd for $C_{22}H_{35}O_{12}$ (M + H) 491, found 491. Anal Calcd for $C_{22}H_{34}O_{12}$: C, 53.86; H, 6.99. Found: C, 53.92; H, 7.13.

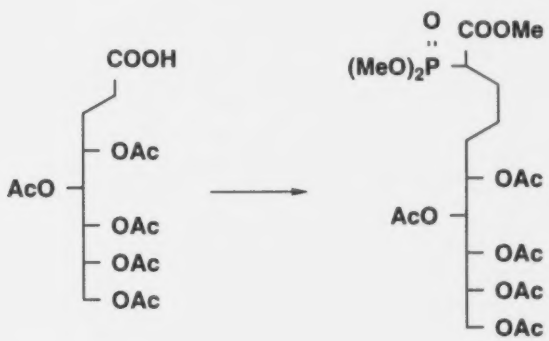
4,5,6,7,8-Penta-*O*-acetyl-2,3-dideoxy-D-*glucoo*ctanoic acid (154).



TFA (2 mL) was added to a stirred solution of monosaccharide **153** (0.446 g, 0.909 mmol) in CH_2Cl_2 (10 mL)[126] and the reaction was monitored by TLC (silica, 40% EtOAc-

hexane). After 3 h, no starting material remained and the solvent was evaporated. The residue was recrystallized from EtOAc-hexane, affording **154** (347 mg, 87%) as a powder: mp 142 °C; $[\alpha]_D$ = -2.6° (c 2.3, $CHCl_3$); FT-IR ($CHCl_3$ cast) 3600-2800, 1747, 1717, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.70-2.10 (m, 14 H), 2.15 (s, 3 H), 2.39 (ap t, *J* = 7 Hz, 2 H), 4.04-4.32 (m, 2 H), 5.00-5.20 (m, 2 H), 5.21-5.32 (m, 1 H), 5.39-5.48 (m, 1 H), 7.40-7.95 (br s, 1 H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 20.54, 20.72 (two coincident peaks), 20.79 (two coincident peaks), 25.45, 29.19, 61.56, 68.58 (two coincident peaks), 70.47, 71.89, 169.86, 169.95, 170.02, 170.39, 170.60, 177.00; mass (FAB) *m/z* calcd for $C_{18}H_{27}O_{12}$ (M + H) 435, found 435.

6,7,8,9,10-Penta-*O*-acetyl-2,3,4-trideoxy-2-(dimethylphosphono)-D-*glucodecanoic* acid, methyl ester (155).



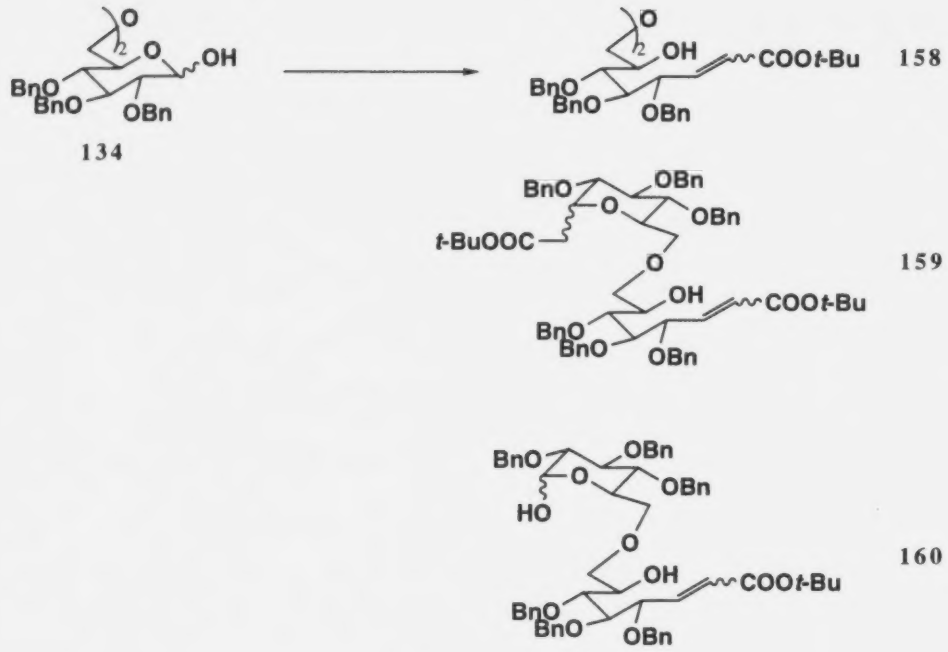
$SOCl_2$ (0.60 mL, 0.97 g, 0.82 mmol) was added to a stirred solution of penta-acetoxy acid **154** (80.3 mg, 0.185 mmol) in dry benzene (5.0 mL) (Ar atmosphere) and the mixture

was heated at 80 °C for 3 h, cooled to room temperature, and evaporated under reduced pressure with protection from moisture. The residue was evaporated from benzene (5 mL) to remove traces of $SOCl_2$, and then dissolved in dry CH_2Cl_2 (5 mL). The mixture was protected from light and sodium *N*-hydroxythiopyridonide (43.0 mg, 0.288 mmol) was added. Stirring was continued for 20 min and then trimethyl 2-phosphonoacrylate (180 μL, 225 mg, 1.16 mmol) was added. The reaction mixture was irradiated (300 W tungsten lamp) for 3 h with continued stirring. The mixture was diluted to a volume of 100 mL with CH_2Cl_2, washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 20% EtOAc-hexane, gave the chain-extended product (143.2 mg): R_f = 0.20.

Bu_3SnH (70 mL, 76 mg, 0.26 mmol) and then AIBN (1.5 mg, 9.3 mmol) were added to a stirred solution of the chain extended product in benzene (5 mL) (Ar atmosphere), and the solution was heated at 85 °C for 24 h and then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using EtOAc, gave **155** (70.0 mg, 63%) as an oil: FT-IR ($CHCl_3$ cast) 1746, 1221, 1050, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, mixture of diastereoisomers) 1.15-1.90 (m, 6 H), 2.00-2.15 (5 x s, 15 H), 2.96 (ap ddd, $^2J_{PH}$ = 16, J = 8, 4 Hz, 1 H), 3.63 (ap d, $^3J_{PH}$ = 8 Hz, 3 H), 3.66 (ap s, 3 H), 3.72 (ap d, $^3J_{PH}$ = 8 Hz, 3 H), 4.05-4.32 (m, 2 H), 4.96-5.09 (m, 2 H), 5.33 (ap

dd, J = 8, 6 Hz, 1 H), 5.39 (ap dd, J = 8, 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz, mixture of diastereoisomers) δ 20.60, 20.66, 20.71, 23.64 (d, $^2J_{PC}$ = 15, C-3), 23.72 (d, $^2J_{PC}$ = 15 Hz, C-3), 26.18, 26.53, 29.93, 29.96, 44.73 (d, $^1J_{PC}$ = 130 Hz, C-2), 44.79 (d, $^1J_{PC}$ = 130 Hz, C-2), 52.56, 52.58, 53.27 (d, $^2J_{PC}$ = 6 Hz, $POCH_3$), 53.39 (d, $^2J_{PC}$ = 6 Hz, $POCH_3$), 61.47, 61.49, 68.69, 68.71, 61.84, 68.91, 70.59, 70.66, 70.83, 70.91, 169.18, 169.21, 169.25, 169.71, 169.72, 169.74, 169.89, 170.21, 170.27, 170.43 (some peaks must be coincident); mass (FAB) *m/z* calcd for $C_{23}H_{37}O_{15}P$ 584, found 584. (The above experimental details are adapted from reference 97.)

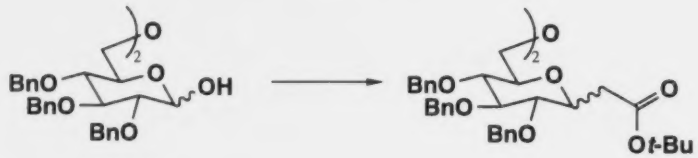
Di[1,1-Dimethylethyl 4,5,6-tri-*O*-benzyl-2,3-dideoxy-D-*gluco*-2-octenoate] 6',6-anhydride (158); [1,1-Dimethylethyl 4,5,6-tri-*O*-benzyl-2,3-dideoxy-D-*gluco*-2-octenoate - 2-(2',3',4'-tri-*O*-benzyl-D-*gluco*pyranosyl)acetic acid, 1,1-dimethylethyl ester] 8,6' anhydride (159); and [1,1-Dimethylethyl 4,5,6-tri-*O*-benzyl-2,3-dideoxy-D-gluco-2-octenoate - (2',3',4'-tri-*O*-benzyl-D-*gluco*pyranose)] 8,6' anhydride (160).



Aqueous NaOH (2 N, 25 mL) was added to a solution of *t*-butyl 2-(triphenylphosphonium)acetate bromide (423 mg, 0.925 mmol) in $CHCl_3$ (25 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and filtered into a flask containing the disaccharide **134** (297 mg, 335 μmol), and the solution was evaporated at room temperature. Dry dioxane (10 mL) was added, and the mixture was then heated at 90 °C for 16 h, and monitored by TLC (35% EtOAc-hexane, silica). The reaction was incomplete and the bath temperature was raised to 110 °C for 24 h. TLC analysis indicated that no starting material was present and several new spots had formed. The reaction mixture was cooled to 50 °C and then evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm),

using 30% EtOAc-hexane, gave **159** (8.7 mg, 3%): R_f = 0.40; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40-1.55 (6 x s, 18 H), 1.70-1.95 (br s, 1 H), 2.55-2.65 (m, 2 H), 3.30-4.05 (m, 11 H), 4.15-4.95 (m, 14 H), 5.75-6.15 (br m, 1 H), 6.57-6.95 (br m, 1 H), 7.12-7.45 (m, 30 H). Continued elution gave compound **158** (67.7 mg, 19%) had: R_f = 0.25; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40-1.55 (ap s, 18 H), 1.50-1.95 (br s, 2 H), 3.44-3.61 (m, 6 H), 3.62-3.71 (m, 2 H), 3.73-3.81 (m, 4 H), 4.11-4.21 (m, 2 H), 4.55-4.98 (m, 12 H), 5.70-80 (m, 0.2 H, *Z* olefin H-2), 5.92-6.07 (m, 0.8 H, *E* olefin H-2), 6.23-6.33 (m, 0.2 H, *Z* olefin H-3), 6.75-6.92 (m, 0.8 H, *E* isomer H-3), 7.12-7.45 (m, 30 H). The material is a mixture of *E* and *Z* isomers 64:32:4 (*EE*:*EZ*:*ZZ*). Fractional integrations have been given for the olefinic signals. Continued elution gave compound **160** (180 mg, 56%) had: R_f = 0.10; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40-1.48 and 1.48-1.55 (br s , 9 H), 1.50-2.50 (br s, 2 H), 3.44-3.80 (m, 7 H), 3.82-4.14 (m, 4 H), 4.35-4.44 (m, 1 H), 4.11-4.21 (m, 2 H), 4.50-5.05 (m, 12 H), 5.10-5.25 (m, 0.67 H, β anomeric), 5.35-5.42 (m, 0.33 H, α anomeric) 5.75-5.85 (m, 0.33 H, *Z* olefin H-2), 5.92-6.07 (m, 0.67 H, *Z* olefin H-2), 6.17-6.32 (m, 0.33 H, *Z* olefin H-3), 6.66-6.95 (m, 0.67 H, *E* isomer H-3), 7.12-7.45 (m, 30 H).

Di[2-(2,3,4-tri-*O*-benzyl-D-*gluco*pyranosyl)acetic acid, 1,1-dimethylethyl ester] 6',6-anhydride (161).



NaOH (2 N, 50 mL) was added to a solution of *t*-butyl 2-(triphenylphosphonium)acetate bromide (5.21 g, 11.4 mmol) in $CHCl_3$ (50 mL) in a separatory funnel and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated to a volume of 10 mL. This solution was added to disaccharide **134** (0.513 g, 0.581 mmol) and 2-pyridone (20 mg) was added. The mixture was heated at 65 °C for 60 h, at which point no starting material was present (^1H NMR, 200 MHz). The solvent was evaporated and flash chromatography of the residue over silica gel (3 x 20 cm), using 35% EtOAc-hexane, gave **161** (0.422 g, 90%): R_f = 0.21; FT-IR (CH_2Cl_2 cast) 3030, 1733, 1153, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, mixture of 3 isomers) δ 0.80-95 (m, 18 H, *t*-Bu), 2.03-2.68 (m, 4 H, CH_2COO), 3.03-4.40 (m, 14 H, C**H**OH and C**H**$_2$OH), 4.50-5.05 (m, 12 H, OCH_2Ph), 7.10-7.40 (m, 30 H, H-Ph); ^{13}C NMR ($CDCl_3$, 75 MHz, mixture of three isomers, only most intense peaks reported) δ 14.08, 14.16, 22.73, 23.03, 23.81, 24.52, 24.85, 25.59, 25.74, 25.86, 25.59, 26.52, 26.79, 27.13, 28.11, 28.98, 29.40, 29.75, 30.08, 30.42, 30.93, 31.97, 32.81, 33.53, 37.15, 37.45, 38.62, 38.80, 39.43, 68.20,

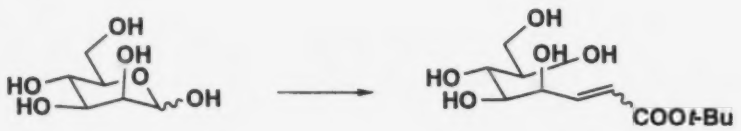
70.38, 72.13, 74.98, 75.14, 75.60, 78.41, 79.10, 80.43, 81.49, 87.12, 126.97, 127.28, 127.63, 127.70, 127.80, 127.87, 127.97, 128.02, 128.45, 128.83, 129.49, 130.90, 138.16, 138.51, 138.64, 170.19.

Di[2,3,4-tri-*O*-benzyl-1-*O*-(triphenylmethyl)-D-*gluco*hexitol] 6'6-anhydride (162).

DIBAL (10.0 mL, 1.0 M in CH_2Cl_2, 10 mmol) was added to a cooled (-78 °C) and stirred solution of disaccharide **134** (297 mg, 0.337 mmol) in CH_2Cl_2 (Ar atmosphere). The bath was removed and stirring continued for 24 h. The solution was cooled (0 °C) and CH_2Cl_2 (50 mL) was added, followed by 2 N HCl which was added until the precipitate of $Al(OH)_3$ dissolved. The organic phase was separated and washed with brine (50 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in dry pyridine (5 mL) and trityl chloride (193 mg, 0.693 mmol) was added. The mixture was stirred at reflux for 2 h and then cooled to room temperature. The pyridine was evaporated and the residue was dissolved in $CHCl_3$ (50 mL). The solution was washed with 2 N HCl (50 mL), and brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10%

EtOAc-hexane, gave **162** as an oil (178 mg, 37%): R_f = 0.10; FT-IR ($CHCl_3$ cast) 3500-3100, 3086, 3059, 3030, 1596, 1153, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.01 (d, *J* = 8 Hz, 2 H), 3.22-3.44 (m, 8 H), 3.62-3.66 (m, 2 H), 3.89-3.94 (m, 4 H), 3.95-3.99 (m, 2 H), 4.06 (d, *J* = 11 Hz, 2 H), 4.21 (d, *J* = 11 Hz, 2 H), 4.50 (d, *J* = 11 Hz, 2 H), 4.59 (d, *J* = 11 Hz, 2 H), 4.63 (d, *J* = 11 Hz, 2 H), 4.70 (d, *J* = 11 Hz, 2 H), 6.88 (m, 2 H), 7.05-7.49 (m, 58 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 64.36, 64.79, 70.86, 72.86, 73.10, 74.19, 77.45, 78.65, 78.99, 86.73, 126.92, 126.98, 127.30, 127.51, 127.58, 127.76, 127.84, 127.97, 128.04, 128.04, 128.24, 128.27, 128.41, 128.74, 138.02, 138.14, 138.51, 143.90, 143.98 (some aromatic signals must be coincident).

(*E*)-2,3-Dideoxy-D-*manno*-2-octenoic acid, 1,1-dimethylethyl ester (165).



Aqueous NaOH (2 N, 25 mL) was added to a solution of *t*-butyl 2-(triphenylphosphonium)acetate bromide (4.70 g, 10.3 mmol) in $CHCl_3$ (25 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry dioxane (50 mL), and D-mannose (1.82 g, 10.0 mmol) was

added. The mixture was then heated at 70 °C for 2 h. (In this experiment temperature control is not critical, but the proportion of *E*-isomer falls at a higher temperature.) The mixture was cooled to room temperature and then evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (50 mL). The layers were separated and the water was extracted with CH_2Cl_2 (1 x 50 mL). The aqueous phase was evaporated and the residue was recrystallized from MeOH-$CHCl_3$ (by dissolution in MeOH, followed by addition of $CHCl_3$), affording **165** (2.37 g, 85%) as a 2:1 *E*:*Z* mixture of isomers. The product had: mp 153-158 °C; FT-IR (nujol mull) 3600-3100, 1686, 1640, 1174 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.42 (s, 9 H), 3.33-3.77 (m, 5 H), 3.98 (d, *J* = 8 Hz, 0.33 H), 4.05-4.12 (m, 1 H), 4.20-4.77 (m, 3.67 H), 4.97-5.17 (m, 1 H) 5.72 (dd, *J* = 12, 2 Hz, 0.33 H, H-$2_{Z\ isomer}$), 5.89 (dd, *J* = 17, 3 Hz, 0.67 H, H-$2_{E\ isomer}$), 6.23 (dd, *J* = 12, 8 Hz, 0.33 H, H-$2_{Z\ isomer}$), 7.08 (dd, *J* = 17, 4 Hz, 0.67 $H_{E\ isomer}$); ^{13}C NMR (DMSO-d_6, 100 MHz) (signals for *Z* isomer are marked with an asterisk) δ 27.81 (q', $C(CH_3)_3$), 63.76 (t'), 67.07* (d'), 69.64 (d'), 69.80 (d'), 70.70* (d'), 71.15 (d'), 71.31* (d'), 72.07 (d'), 79.42 (s', $OCMe_3$), 79.95* (s', $OCMe_3$), 120.97 (d', C-3), 121.36* (d', C-3) , 150.04* (d', C-2), 151.03 (d', C-2), 165.33 (s', C-1); mass (CI) *m/z* calcd for $C_{12}H_{22}O_7$ 278, found 296 (M + 18). Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 51.34; H, 7.90.

Fractional crystallization from EtOH, gave a mixture rich in the *Z* isomer, and evaporation of the mother liquor

afforded the *E* isomer (42% recovery): mp 161-162 °C; $[\alpha]_D$ = +33° (c 0.91, water); FT-IR (nujol mull) 3500-3100, 1686, 1640, 1174 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.52 (s, 9 H, $C(CH_3)_3$), 3.61-3.88 (m, 5 H), 4.35-4.41 (m, 1 H, H-4), 6.08 (dd, *J* = 16, 2 Hz, 1 H, H-2), 7.05 (dd, *J* = 16, 6 Hz, 1 H, H-3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 27.86 (q', $C(CH_3)_3$), 63.81 (t', C-8), 69.67 (d'), 69.84 (d'), 71.19 (d'), 72.11 (d'), 79.47 (s', $OCMe_3$), 121.00 (d', C-2), 151.07 (d', C-3), 165.37 (s', C-1); mass (CI) *m/z* calcd for $C_{12}H_{22}O_7$ 278, found 296 (M + 18). Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 51.34; H, 7.90.

(*E*)-2,3-Dideoxy-D-*galacto*-2-octenoic acid, 1,1-dimethylethyl ester (166).

Aqueous NaOH (2 N, 25 mL) was added to a solution of *t*-butyl 2-(triphenylphosphonium)acetate bromide (4.70 g, 10.3 mmol) in $CHCl_3$ (25 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry dioxane (50 mL), and D-galactose (1.82 g, 10.0 mmol) was added. The mixture was then heated at 95 °C for 10 h, care being taken not to exceed this temperature. The mixture was

cooled to room temperature and then evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (50 mL). The layers were separated and the water was extracted with CH_2Cl_2 (1 x 50 mL). The aqueous phase was evaporated and the residue was recrystallized from MeOH-$CHCl_3$ (by dissolution in MeOH, followed by addition of $CHCl_3$), affording **166** (2.13 g, 76%), which contained < 5 mol % water (^{1}H NMR) even after storage under high vacuum for 5 days. The material had: mp 143-145 °C; $[\alpha]_D$ = -5° (c 1.8, water); FT-IR (nujol mull) 3600-3100, 1693, 1646, 1197, 1172 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 1.52 (s, 9 H, $C(CH_3)_3$), 3.60-3.85 (m, 4 H), 3.92-3.99 (m, 1 H), 4.61-4.67 (m, 1 H, H-4), 6.08 (dd, *J* = 17, 2 Hz, 1 H, H-2), 6.99 (dd, *J* = 17, 4 Hz, 1 H, H-3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 27.81 (q', $C(CH_3)_3$), 62.95 (t', C-8), 69.55 (d'), 69.87 (d', two peaks), 71.87 (d'), 79.42 (s', $OCMe_3$), 121.38 (d', C-2), 150.67 (d', C-3), 165.19 (s', C-1); exact mass *m/z* calcd for $C_{11}H_{19}O_7$ (M - CH_3) 263.1131, found 263.1123.

(*E*)-4-Acetamido-2,3,4-trideoxy-D-2-*glucooctenoic* acid, 1,1-dimethylethyl ester (167).

Aqueous NaOH (2 N, 25 mL) was added to a solution of *t*-butyl 2-(triphenylphosphonium)acetate bromide (4.70 g, 10.3 mmol) in $CHCl_3$ (25 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry 1:1 dioxane-DMF (50 mL), and 2-acetamido-2-deoxy-D-*gluco*pyranose (2.22 g, 10.0 mmol) was added. The mixture was then heated at 90 °C for 4 h, cooled to room temperature, and evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (50 mL). The layers were separated and the water was extracted with CH_2Cl_2 (2 x 25 mL). The aqueous phase was evaporated and the residue was swirled and warmed with 1:1 EtOH:$CHCl_3$ (75 mL). The insoluble material [2-acetamido-2-deoxy-D-glucopyranose (0.153 g)] was filtered off and the filtrate was evaporated. The new residue was dissolved in hot $CHCl_3$ (50 mL) and the solution was cooled to room temperature, and hexane was added to precipitate a further crop (215 mg) of starting material. Evaporation of the mother liquor gave material (2.61 g) which was crystallized from EtOH-$CHCl_3$ (by dissolution in EtOH, followed by addition of $CHCl_3$), to afford **167** (1.29 g, 41%, 48% corrected for recovered 2-acetamido-2-deoxy-α-D-glucopyranose): mp 171-172 °C; $[\alpha]_D$ = +30° (c 2.0, water); FT-IR (KBr disk) 3550-3100, 1690, 1649, 1154 cm^{-1}; ^1H NMR (1% DMSO-d_6 in D_2O, 300 MHz) δ 1.48 (s, 9 H, $OC(CH_3)_3$), 2.06 (s, 3 H, N-$COCH_3$), 3.54 (dd, *J* = 8, 3 Hz, 1 H), 3.57-3.78 (m, 2 H), 3.83 (dd, *J* = 12, 3 Hz, 1 H), 3.96 (dd, *J* = 8, 2 Hz, 1 H),

4.68 (dd, J = 8, 8 Hz, 1 H, H-4), 5.99 (d, J = 17 Hz, 1 H, H-2), 6.82 (dd, J = 17, 8 Hz, 1 H, H-3); ^{13}C NMR (D_2O, 75 MHz) δ 22.81 (q', acetate methyl), 28.12 (q', $C(CH_3)_3$), 54.34 (d', C-4), 63.68 (t', C-8), 71.24 (d', two coincident peaks), 72.80 (d'), 83.71 (s', $OCMe_3$), 125.14 (d', C-2), 144.54 (d', C-3), 168.40 (s', C-1), 174.83 (s', N-COMe); exact mass m/z calcd for $C_{14}H_{26}NO_7$ (M + H) 320.1709, found 320.1711. Anal. Calcd for $C_{14}H_{25}NO_7$: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.58; H, 7.81; N, 4.33.

(*E*)-2,3-Dideoxy-D-*ribo*-2-heptenoic acid, 1,1-dimethylethyl ester (168).

Aqueous NaOH (2 N, 25 mL) was added to a solution of *t*-butyl 2-(triphenylphosphonium)acetate bromide (4.70 g, 10.3 mmol) in $CHCl_3$ (25 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry 1:1 dioxane-DMF (25 mL), and D-ribose (1.51 g, 10.1 mmol) was added. The mixture was then heated at 75 °C for 4 h, cooled to room temperature, and evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (50 mL). The layers were separated and the water was extracted with CH_2Cl_2 (2 x 50 mL). The aqueous phase was evaporated,

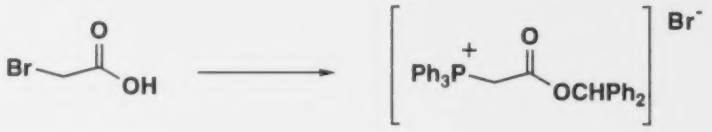
dissolved in MeOH (50 mL), and re-evaporated. This procedure of evaporation from MeOH was repeated once more. The residue was then swirled with 1:1 Et_2O:hexane (200 mL) and the mixture set aside for 24 h. The resulting solid (2.12 g) was filtered off and recrystallized from $CHCl_3$-hexane (by dissolution in $CHCl_3$, followed by addition of hexane), affording **168** (1.45 g, 58%), containing <5% (^1H NMR) of the *Z* isomer: mp 104-105 °C; $[\alpha]_D$ = -33° (c 2.7, water); FT-IR (MeOH cast) 3550-3100, 1743, 1331 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,) δ 1.48 (s, 9 H, $C(CH_3)_3$), 3.28-3.46 (m, 4 H), 3.47-3.61 (m, 1 H), 4.26-4.33 (m, 1 H), 4.38 (t, *J* = 6 Hz, 1 H), 4.69 (d, *J* = 6 Hz, 1 H), 4.78 (d, *J* = 6 Hz, 1 H), 5.06 (d, *J* = 6 Hz, 1 H), 5.86 (dd, *J* = 17, 2 Hz, 1 H, H-2), 6.90 (dd, *J* = 17, 6 Hz, 1 H, H-3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 27.79 (q', $C(CH_3)_3$), 63.23 (t', C-7), 70.86 (d'), 72.45 (d'), 74.58 (d'), 79.45 (s', $OCMe_3$), 121.91 (d', C-2), 148.47 (d', C-3), 165.17 (s', C-1); mass (CI) *m/z* calcd for $C_{11}H_{20}O_6$ 248, found 266 (M + 18). Anal. Calcd for $C_{11}H_{20}O6$: C, 53.22; H, 8.12. Found: C, 53.38; H, 8.26.

(*E*)-2,3-Dideoxy-D-*arabino*-2-heptenusonic acid, 1,1-dimethylethyl ester (169).

Aqueous NaOH (2 N, 25 mL) was added to a solution of *t*-butyl 2-(triphenylphosphonium)acetate bromide (4.70 g, 10.3 mmol) in $CHCl_3$ (25 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry 1:1 dioxane-DMF (25 mL), and D-arabinose (1.50 g, 10.0 mmol) was added. The mixture was then heated at 75 °C for 4 h, cooled to room temperature, and then evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (50 mL). The layers were separated and the water was extracted with CH_2Cl_2 (2 x 50 mL). The aqueous phase was evaporated, dissolved in MeOH (50 mL) and re-evaporated again. This procedure of evaporation from MeOH was repeated once more. The residue was dissolved in Et_2O (300 mL) and the solution was set aside for 24 h. The solid was filtered off and recrystallized from $CHCl_3$-hexane (by dissolution in $CHCl_3$, followed by addition of hexane), affording **169** (2.29 g, 92%): mp 146-147 °C; $[\alpha]_D$ = +7° (c 1.7, water); FT-IR (MeOH cast) 3550-3100, 1702 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 1.48 (s, 9 H, $C(CH_3)_3$), 3.46-3.53 (m, 2 H), 3.58-3.63 (m, 1 H), 3.67 (dd, *J* = 11, 3 Hz, 1 H), 4.41-4.46 (m, 1 H, H-4), 5.92 (ddd, *J* = 16, 3, 1 Hz, 1 H, H-2), 6.81 (ddd, *J* = 16, 6, 1 Hz, 1 H, H-3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 29.00 (q', $C(CH_3)_3$), 64.51 (t', C-7), 71.53 (d'), 72.57 (d'), 74.28 (d'), 84,30 (s', $OCMe_3$), 124.59 (d', C-2), 149.80 (d', C-3), 169.51 (s', C-1); mass (CI) *m/z* calcd for $C_{11}H_{20}O_6$ 248, found 266 (M +

18). Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.35; H, 8.13.

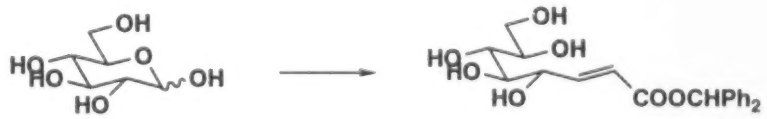
Diphenylmethyl 2-(Triphenylphosphonium)acetate bromide (170).



Anhydrous Et_2O (200 mL) was added to a stirred mixture of benzophenone hydrazone (13.03 g, 66.4 mmol), Na_2SO_4 (15.51 g, 119 mmol), and yellow HgO (35.20 g, 162 mmol) under Ar. Saturated anhydrous ethanolic KOH (5.0 mL) was added, and stirring was continued for 75 min.[127] The wine-colored solution was then added dropwise to a stirred and cooled (0 °C) solution of 2-bromoacetic acid in acetone. Stirring was continued overnight, the solution was diluted to 300 mL with Et_2O, and then washed with aqueous NaOH (2 N, 1 x 200 mL), and with brine (1 x 200 mL). The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in Et_2O (200 mL), and Ph_3P (19.00 g, 72.4 mmol) was added. The mixture was stirred for 24 h, and the precipitate was filtered off to afford the phosphonium bromide salt (24.92 g, 60%). The mother liquor was stirred for an additional 24 h, affording another batch (6.93 g, 16%, total 76%) of the product **170**. The salt, **170**, does not melt, but decomposes

at 170 °C and had: FT-IR (nujol mull) 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.73 (d, $^2J_{PH}$ = 14 Hz, 2 H, H-2), 6.69 (s, 1 H, $OCHPh_2$), 7.14-7.34 (m, 11 H, Ar-H), 7.50-6.57 (m, 6 H, Ar-H), 7.66-7.84 (m, 8 H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.33 (dt', $^1J_{PC}$ = 55 Hz, 1 C, C-2), 79.85 (s', $OCHPh_2$), 117.77 (ds', $^1J_{PC}$ = 88 Hz, 1 C, Ar_{ipso}), 127.24 (d'), 128.18 (d'), 128.59 (d'), 130.10 (d'), 130.27 (d'), 133.94 (d'), 135.03 (dd', $^2J_{PC}$ = 12 Hz, Ar_{ortho}), 138.64 (s', C_{ipso} of diphenylmethyl), 163.73 (ds', $^2J_{PC}$ = 4 Hz, C-1); exact mass *m/z* calcd for $C_{33}H_{27}O_2P$ (M - HBr) 486.1748, found 486.1743. Anal. Calcd for $C_{33}H_{28}BrO_2P$: C, 69.85; H, 4.97. Found: C, 69.69; H, 5.02.

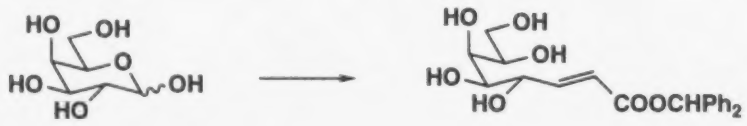
(*E*)-2,3-Dideoxy-D-*gluco*-2-octenoic acid, diphenylmethyl ester (171).



Aqueous NaOH (2 N, 75 mL) was added to a solution of diphenylmethyl 2-(triphenylphosphonium)acetate bromide **170** (6.15 g, 10.8 mmol) in $CHCl_3$ (75 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry 1:1 dioxane-DMF (25 mL), and D-glucose (1.82 g, 10.1 mmol) was added. The mixture was then heated at 90 °C for 3 h, cooled to room temperature, and then evaporated.

The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (100 mL), and the resulting emulsion was allowed to stand for 24 h, by which time the solid product had collected at the interface of the two immiscible liquids. The material was filtered off and recrystallized from MeOH-water (by dissolution in MeOH, followed by addition of water), affording **171** (3.29 g, 85%): mp 139-140 °C; $[\alpha]_D$ = -13° (c 1.2, MeOH); FT-IR (MeOH cast) 3550-3100, 1723, 1654, 1144 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.31-3.69 (m, 5 H), 4.24-4.36 (m, 2 H, H-4 and OH), 4.41 (d, *J* = 7 Hz, 1 H), 4.46 (d, *J* = 6 Hz, 1 H), 4.56 (d, *J* = 7 Hz, 1 H), 5.20 (d, *J* = 6 Hz, 1 H), 6.13 (dd, *J* = 18, 3 Hz, 1 H, H-2), 6.85 (s, 1 H, $CHPh_2$), 7.15 (dd, *J* = 18, 6 Hz, 1 H, H-3), 7.24-7.49 (m, 10 H, H-Ar); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 63.32 (t', C-8), 70.65 (d'), 71.23 (d'), 72.14 (d'), 72.30 (d'), 76.09 (d'), 119.24 (d', C-2), 126.46 (d'), 126.50 (d'), 127.72 (d'), 128.51 (d'), 140.60 (s', $C_{ipso}Ar$), 150.94 (d', C-3), 164.80 (s', C-1) (expected 17 peaks, two must be coincident); exact mass *m/z* calcd for $C_{21}H_{22}O_6$ (M - H_2O) 370.1416, found 370.1416. Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 64.87; H, 6.01.

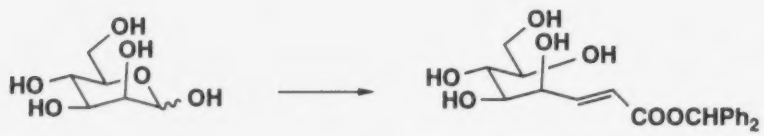
(*E*)-2,3-Dideoxy-D-*galacto*-2-octenusonic acid, diphenylmethyl ester (172).



Aqueous NaOH (2 N, 75 mL) was added to a solution of diphenylmethyl 2-(triphenylphosphonium)acetate bromide **170** (6.15 g, 10.8 mmol) in $CHCl_3$ (75 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry 1:1 dioxane:DMF (25 mL), and D-galactose (1.82 g, 10.1 mmol) was added. The mixture was then heated at 90 °C for 3 h, cooled to room temperature, and then evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (100 mL), and the resulting emulsion was allowed to stand for 24 h, at which time the solid product had collected at the interface of the two immiscible liquids. The material was filtered off and recrystallized from MeOH-water (by dissolution in MeOH, followed by addition of water), affording **172** (2.32 g, 60%): mp 171-172 °C; $[\alpha]_D$ = -10° (c 0.73, MeOH); FT-IR (MeOH cast) 3550-3100, 1711, 1666, 1168 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.36-3.60 (m, 4 H), 3.69-3.77 (m, 1 H), 4.22 (d, *J* = 7 Hz, 1 H), 4.25 (d, *J* = 7 Hz, 1 H), 4.44-4.60 (m, 3 H), 4.90 (d, *J* = 7 Hz, 1 H), 6.17 (dd, *J* = 17, 3 Hz, 1 H, H-2), 6.87 (s, 1 H, $CHPh_2$), 7.17 (dd, *J* = 17, 6 Hz, 1 H, H-3), 7.22-7.47 (m, 10 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 63.02 (t', C-8), 69.57 (d'), 69.88 (d'), 70.11 (d'), 71.87 (d'), 76.13 (d'), 119.48 (d', C-2), 126.48 (d'), 126.55 (d'), 127.75 (d'), 128.54 (d'), 140.65 (s', Ar_{ipso}), 153.04 (d', C-3), 164.78 (s', C-1) (expected 17 peaks, three must be coincident); mass (CI) *m/z* calcd for $C_{21}H_{24}O_7$ 388,

found 406 (M + 18). Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.92; H, 6.23. Found: C, 65.23; H, 6.16.

(*E*)-2,3-Dideoxy-D-*manno*-2-octenusonic acid, diphenylmethyl ester (173).



Aqueous NaOH (2 N, 75 mL) was added to a solution of diphenylmethyl 2-(triphenylphosphonium)acetate bromide **170** (6.20 g, 10.9 mmol) in $CHCl_3$ (75 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in dry dioxane (30 mL), and D-mannose (1.82 g, 10.1 mmol) was added. The mixture was then heated at 90 °C for 6 h, cooled to room temperature, and then evaporated. The residue was shaken with a mixture of water (100 mL) and CH_2Cl_2 (100 mL), and the resulting emulsion was allowed to stand for 24 h, at which time the solid product had collected at the interface of the two immiscible liquids. The material was filtered off and recrystallized from MeOH-water (by dissolution in MeOH, followed by addition of water), affording **173** (2.84 g, 73%) which had: mp 152-155 °C; $[\alpha]_D$ = 13° (c 0.73, MeOH); FT-IR (MeOH cast) 3550-3100, 1716, 1652, 1170 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.33-3.68 (m, 5 H),

4.15-4.23 (m, 1 H), 4.31 (d, J = 6 Hz, 1 H), 4.38 (dd, J = 6, 6 Hz, 1 H), 4.47 (d, J = 5 Hz, 1 H), 4.56 (d, J = 6 Hz, 1 H), 5.23 (d, J = 7 Hz, 1 H), 6.16 (dd, J = 17, 3 Hz, 1 H, H-2), 6.88 (s, 1 H), 7.21-7.70 (m, 11 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 63.78 (t', C-8), 69.65 (d'), 69.90 (d'), 71.12 (d'), 72.07 (d'), 76.08 (d'), 118.95 (d', C-2), 126.48 (d'), 127.73 (d'), 128.52 (d'), 140.62 (s',C_{ipso}Ar), 153.38 (d', C-3), 164.85 (s', C-1) (expected 17 peaks, four must be coincident); mass (CI) m/z calcd for $C_{21}H_{24}O_7$ 388, found 406 (M + 18). Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.92; H, 6.23. Found: C, 64.92; H, 6.27. Traces of the E isomer were visible in ^{1}H NMR.

2,3-Dideoxy-D-*mannooctanoic* acid, γ-lactone (174).

A 2:1 mixture of (*E*)- and (*Z*)-2,3-dideoxy-2-D-manno-octenusonic acid *t*-butyl ester (**165**) (0.920 g, 3.31 mmol) in absolute EtOH (100 mL) was hydrogenated in a Parr shaker at 55 psi, using 10% Pd/C (100 mg). After 16 h, the catalyst was filtered off, and TFA (10 mL) was added. The resulting solution was refluxed for 1 h, cooled to room temperature and evaporated. The residue was covered with 1:1 EtOH:toluene (25 mL), and evaporation then gave the crude product, which was recrystallized from EtOH, to afford **174** (0.671 g, 98%):

mp 155-156 °C (lit.[116] 156-157 °C); $[\alpha]_D$ = -15° (c 0.52, EtOH) [lit.[@116] -16.6° (c not specified, EtOH)]; FT-IR (MeOH cast) 3550-3100, 1770, 1110 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 2.27-2.37 (m, 1 H, H-2), 2.41-2.51 (m, 1 H, H-2), 2.64-2.77 (m, 2 H, H-3), 3.67-3.72 (m, 2 H), 3.77-3.82 (m, 1 H), 3.89 (dd, *J* = 12, 4 Hz, 1 H), 4.02 (dd, *J* = 7, 2 Hz, 1 H), 4.77 (ddd, *J* = 7, 7, 7 Hz, 1 H); ^{13}C NMR (D_2O, 100 MHz) δ 23.31 (t', C-3), 28.18 (t', C-2), 62.85 (t', C-8), 69.78 (d'), 70.19 (d'), 70.56 (d'), 81.05 (d'), 181.71 (s', C-1); exact mass *m/z* calcd for $C_8H_{15}O_6$ (M + H) 207.0868, found 207.0864. Anal. Calcd for $C_8H_{14}O_6$: C, 46.58; H, 6.85. Found: C, 46.55; H, 6.81.

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Glossary

AIBN	azobis(isobutyronitrile)
AmB	Amphotericin B
ap	apparent
APT	Attached Proton Test
acac	Acetoacetonate
BINAP	1,1'-Bi-2-napthol
Bn	Benzyl
BOC	*t*-Butyloxycarbonyl
CAN	Ceric Ammonium Nitrate
CD	Circular Dichroism
CI	Chemical Ionization
CPK	Corey-Pauling-Koltun (type of space filling molecular models)
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-4,5-dicyano-1,4-benzoquinone
DIBAL	Diisobutylaluminum hydride
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
FAB	Fast Atom Bombardment
HMPA	Hexamethylphosphoric triamide
HPLC	High Pressure Liquid Chromatography
KDO	3-Deoxy-**D**-*manno*-octulosonic acid
LiHMDS	Lithium hexamethyldisilazide
MCPBA	*m*-chloroperbenzoic acid
Ms	Methanesulfonyl

NBS	*N*-bromosuccinimide
NMR	Nuclear Magnetic Resonance
OTf	Trifluoromethanesulfonate
PPA	Polyphosphoric acid
QSAR	Quantitative Structure Activity Relationships
TBAF	Tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBPS	*t*-butyldiphenylsilyl
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Tr	Triphenylmethyl (Trityl)